A REPORT ON MULTIPLE CHEMICAL SENSITIVITY (MCS)

The Interagency Workgroup on Multiple Chemical Sensitivity

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Predecisional Draft

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Foreword

Multiple chemical sensitivity (MCS) is the term most commonly applied to a condition that challenges patients, health-care providers, and health and environmental agencies alike. Persons reported as suffering from MCS present with outcomes that range from minor discomfort to severe disability. However, many scientists and medical specialists continue to debate the validity of MCS as a distinct disease entity.

In 1995, because of concern for the health and well-being of persons with symptoms of MCS and because MCS presents challenging policy issues, several federal agencies that conduct or sponsor environmental programs formed the Interagency Workgroup on Multiple Chemical Sensitivity (referred to as "the workgroup" in this report). The workgroup reviewed relevant scientific literature, considered recommendations previously issued by various expert panels, reviewed current and past federal actions, and developed technical and policy recommendations concerning MCS.

This report was prepared by the workgroup's members and staff listed in Sections XIII and XIV. The draft was reviewed by 12 experts in occupational and/or environmental medicine, toxicology, immunology, psychology, psychiatry, and physiology. The subsequent revision was made available as a draft report for the public's review and comment.

The workgroup considers policy makers and researchers at agencies concerned with MCS to be the primary audience for this report. It is not intended to provide guidelines for individual clinical management of those with symptoms of MCS, nor is it intended to evaluate existing diagnostic and treatment methods. Rather, it provides a public health evaluation of the extent and nature of this complex problem and recommends future actions for federal agencies to consider.

The federal departments and agencies represented on the workgroup included the Department of Defense, Department of Energy, Department of Health and Human Services (i.e., Agency for Toxic Substances and Disease Registry, National Center for Environmental Health, National Institute for Occupational Safety and Health, and National Institute of Environmental Health Sciences), Department of Veterans Affairs, and the U.S. Environmental Protection Agency.

Table of Contents

List of Tables

EXECUTIVE SUMMARY

The workgroup reviewed the scientific literature pertinent to multiple chemical sensitivity (MCS), considered recommendations from various expert panels on MCS, reviewed past and current federal actions, and developed technical and policy recommendations. The workgroup considers policy makers and researchers at agencies concerned with MCS issues to be the primary audience for this report.

It is currently unknown whether MCS is a distinct disease entity and what role, if any, the biochemical mechanisms of specific chemicals have in the onset of this condition. The workgroup finds that MCS is currently a symptom-based diagnosis without supportive laboratory tests or agreed-upon signs of clinical manifestation. The workgroup knows of no reports in the literature of definite end-organ damage attributable to MCS. However, scientific knowledge changes over time as additional findings are reported. It is therefore important not to lose sight of lessons from the past in which suspected health effects of environmental exposures were verified at a later date through scientific research.

Summary Findings

- No single accepted case definition of MCS has been established; proposed definitions all differ in key criteria, and some definitions suggest a broad spectrum of possible symptoms. The validated epidemiologic data required to clarify the natural history, etiology, and diagnosis of MCS are not available.

- Several limitations are found in the design of many published MCS studies. Outcome measures in some studies may be influenced by bias in subject selection, lack of investigator blinding during patient assessment, and inconsistent quality assurance of laboratory determinations. Certain outcome measures (e.g., functional imaging techniques) are investigative research tools and need validation by additional studies.

- The workgroup finds that there are few data on the prevalence of MCS. Only three studies have reported the prevalence of self-reported physician-diagnosed MCS. The prevalence of self-reported physician-diagnosed MCS ranges from published values of 0.2 percent in college students to 4.0 percent in elderly persons and an unpublished value of 6 percent among randomly selected California residents.

- The amount of ongoing MCS-specific research conducted or otherwise supported by the federal government is confined to a limited effort by the National Institutes of Health, National Institute of Environmental Health Sciences (NIEHS). Other than the workgroup on MCS, there appears to be no other federal government group convened expressly to examine MCS as a medical entity of relevance to occupational and environmental health. Although there is ancillary research at NIEHS, the Department of Veterans Affairs (DVA), and the U.S. Environmental Protection Agency (EPA) concerning the potential relevance of advancing the scientific database on MCS, no federal effort formulates and oversees a collaborative MCS research plan.

- The major recommendations from several expert workshops held since 1990 are still appropriate. These recommendations, if addressed, should advance the public health response to the public's concerns about MCS.

- Information on the fiscal cost of MCS to society is scarce. The fiscal outlay required for or involved in medical diagnosis and treatment of MCS needs additional study.

- Only limited efforts are being made within federal health and environmental agencies to communicate to health-care providers what is known and not known about MCS; these efforts are primarily being made by the Agency for Toxic Substances and Disease Registry (ATSDR). This lack of education for health-care providers is accompanied by increasing public concern about MCS.

- Numerous therapies aimed at treating MCS have been identified in the literature; however, no widely accepted protocols are proven to be effective in addressing MCS symptomatology. Therapeutic interventions that claim to effectively address or minimize these impacts need objective study and validation.

- While study and validation of therapeutic interventions continue, the goal of patient care should be to promote health without causing harm.

The workgroup concluded that the subject of MCS is unlikely to receive extensive research support as a single entity. Existing personnel and budgetary resources are constrained, and federal agencies

are attempting concurrently to evaluate a variety of syndromes that present with disabling symptoms but lack objective clinical or laboratory evidence of disease. Examples include chronic fatigue syndrome, fibromyalgia, Persian Gulf War-related illnesses, and diseases diagnosed as chronic subclinical infections.

The workgroup identified the need for an overall strategic plan for these syndromes, including MCS, because of scientific uncertainties and unclear public health relevance that attend each syndrome. The strategic plan should articulate the goals and objectives of the research effort, offer guidance on the priorities and sequence for studies, present the critical elements of study design, and reflect on appropriate resource levels. Persons involved in the strategic planning of research should have a broad range of knowledge and experience and represent a variety of scientific disciplines. Public input should be a vital component of this process.

In the context of an overall research strategy, a number of research areas pertinent to MCS were discussed by the workgroup. These areas are found in Section IX and are suggested for consideration for their relevance as part of any MCS strategic plan.

Policy Recommendations for Consideration

The scientific literature is currently inadequate to enable determination of the associations between human exposure(s) to chemicals in the environment and the development or exacerbation of MCS. Targeted research would reduce this uncertainty. Increased scientific knowledge about MCS and the role of environmental chemicals will inevitably be put into the context of benefits and risk.

Virtually all chemicals in use convey both benefits and risks. Every technology, no matter how beneficial, can exert a negative impact on some sector(s) of society. Many chemicals have well-established toxicologic and allergenic properties; undoubtedly, others will be found to have adverse effects in the future. Public health leaders and other risk managers have an obligation to ensure that the benefits of technologies justify the risks. The public health *vision* is health for the entire population. The *reality* of public health will always involve balancing maximum benefit and minimum harm to the public's health and well-being. Risk managers faced with decisions regarding MCS are offered the following policy recommendations by the workgroup:

- Because of the public health issues and challenges presented by MCS, it is recommended that phased efforts be initiated to conduct the targeted research described in the previous

section. A phased approach would make the greatest use of available resources, and at the same time, answer key questions such as prevalence and basic mechanisms of action that would guide follow-up research.

- There is a need to better inform the health-care community about MCS. Health agencies should consider a focused, limited effort in clinician education and awareness.

- Persons should not be offered ineffective, costly, or potentially dangerous treatments. Appropriate care for well-characterized medical and psychological illnesses should not be withheld or delayed. The ramifications of recommending functional changes in workplace or home settings should be considered carefully. Persons identified as having MCS also need education about what is known and not known about MCS.

- There is need for a continuing effort in interagency coordination, whether through the workgroup or a successor group.

- An overall strategic plan for MCS and related syndromes is needed. The strategic plan should articulate the research effort and offer guidance on communication and education of health- care providers and persons experiencing symptoms of MCS.

- The Environmental Health Policy Committee of the Department of Health and Human Services appears to be an appropriate body for overseeing the development of an improved science database on MCS and attendant public health responses.

I. Background and Historical Review

Introduction and History

The condition now most commonly known as multiple chemical sensitivity (MCS) was brought to the attention of the U.S. medical establishment when the late Theron Randolph, a physician trained in allergy and immunology, reported that a number of his patients reacted adversely to chemicals in their environment (Randolph, 1952). He compared the condition to Selye's stress-oriented general adaptation syndrome (Kurt, 1995) and linked the adverse effects of this "petrochemical problem" to contact with chemicals found in commonly encountered substances such as cosmetics, auto fuels, exhaust fumes, and food additives. He also observed that many of his patients reacted to many industrial solvents found in small amounts in manufactured products such as construction materials, newspaper and other ink-related products, furniture, and carpet.

Although Randolph and other physicians who shared his theories published articles in the medical literature during the 1950s and early 1960s, his views were not widely accepted among physicians, particularly those trained in allergy and immunology. In 1965, in response to this lack of acceptance within his specialty, he founded the Society for Human Ecology and invited physicians of all specialties (who were later often referred to as clinical ecologists) to take part. In 1985, the Society changed its name to the American Academy of Environmental Medicine (AAEM, 1992). Today, members are referred to as environmental physicians. However, the term clinical ecologist remains in use.

The American Academy of Environmental Medicine has stated that a wide variety of symptoms, stemming from many different organs, "[m]ay all be the result of biologic system dysfunctions triggered by environmental stressors in susceptible patients" (AAEM, 1992). AAEM supports the application of a comprehensive model of environmental medicine to elucidate the nature of these system dysfunctions. The model states the following:

> Environmentally Triggered Illnesses (EI) result from a disruption of homeostasis by environmental stressors. This disruption may result from a wide range of possible exposures, ranging from a severe acute exposure to a single stressor to cumulative relatively low grade exposures to many stressors over time. The disruption can affect any part of the body via dysfunctioning of any number of the body's many biologic mechanisms and systems. The ongoing manifestations of Environmentally Triggered

> Illnesses are shaped by the nature of stressors and the timing of exposures to them, by the biochemical individuality of the patient, and by the dynamic interactions over time resulting from various governing principles such as **the total load, the level of adaptation, the bipolarity of responses, the spreading phenomenon, the switch phenomenon, and individual susceptibility (biochemical individuality)** (AAEM emphasis) (AAEM, 1992).

There has been increasing debate over MCS in the years since Randolph's publications. A wide variety of symptoms have been reported, including fatigue, malaise, difficulty concentrating, loss of memory, weakness, headaches, nausea, mucous membrane irritation, and dizziness (Terr, 1986; Lax and Henneberger, 1995). MCS patients have associated their symptoms with many substances, including colognes and perfumes, aerosol air freshener, laundry detergent, gasoline exhaust, cleaners, insecticide sprays, and cigarette smoke (Ziem, 1992; Lax and Henneberger, 1995). MCS has been associated with exposure to many kinds of substances. These exposures may occur in workplaces, homes, and outdoors. In this report, the environment in which MCS might occur comprises all these locations.

Topics that have been debated include: whether MCS is a distinct disease entity, its etiology (or etiologies), its pathophysiology, how to define the condition, how it should be treated, and how it should be approached in the legal and legislative arenas. The condition has become more visible through increased media attention. One result of this visibility has been an increase in the number of scientists and physicians taking part in the debate. The discussions have, at times, become contentious, and there have been calls for governmental action by MCS patients, advocacy groups, and legislators.

In recent years, federal agencies have increased their interagency cooperation on MCS issues through sharing of current knowledge, development of research recommendations, and cosponsorship of workshops and conferences. This report is part of that continuing effort.

Terminology

Many other names have been applied to the condition called MCS. Among them are environmental illness (EI), ecological illness, total allergy syndrome, the 20th Century disease (e.g., Hileman, 1991), and idiopathic environmental intolerances (IPCS, 1996). The last term, which is discussed in Section VI, was recommended by a MCS workshop that was organized by the International

Program on Chemical Safety (a program cosponsored by the United Nations Environmental Program, the International Labor Office, and the World Health Organization).

Until more is known about the etiology of the condition, it is not possible to determine what name would be both descriptive and physiologically correct. The workgroup has elected to use the most commonly applied term "multiple chemical sensitivity" ("MCS") throughout this report.

Definitions

The most basic disagreement surrounding the study of MCS has been how to define the condition in ways acceptable to the many interested parties. In 1987, Mark Cullen, M.D., a professor of medicine and epidemiology at Yale University, edited an issue of *Occupational Medicine State of the Art Reviews* entitled "Workers With Multiple Chemical Sensitivities" (Cullen, 1987). He described the case of a middle-aged man who had developed sensitivities to a wide variety of chemicals, including common household products. This occurred after the patient had developed pneumonia following exposure to a chemical spilled at work. Cullen reported his lack of success in treating the patient and noted that there were other patients in whom the same symptoms developed following similar situations. From this experience, Cullen proposed a definition that has become the one most commonly referenced, and is, for some, the *de facto* definition of MCS.

Table 1 presents Cullen's definition and others that have been proposed. Common elements in the definitions are summarized in Table 2. Not shown in Table 2 is the definition used by Kurt (1995) in his research. He defined MCS as "[a] symptom complex triggered by odor or a perceived exposure; occurring at exposure levels below those of allergic sensitivity or irritation; analogous to the symptoms of panic disorder as defined by (DSM-III-R)[1]; lacking objective clinical pathologic criteria; and responsive to panic disorder management." This definition is distinctly different from those in Table 2, (i.e., it is primarily based on psychological criteria); therefore it was not included in the table.

[1] Diagnostic and Statistical Manual, version III. (American Psychiatric Association., 1987)

Table 1: Proposed Definitions for Multiple Chemical Sensitivity (MCS) since 1985.

1985	ad hoc Committee, Ontario Ministry of Health:
	More than 3 months duration
	Multisystem disorder
	Intolerance to foods, chemicals, environmental agents at levels generally tolerated by majority
	No objective physical findings; no consistently altered laboratory test
	Symptoms diminish with avoidance; recur with exposure
1987	Cullen:
	Multiple chemical sensitivities is an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with symptoms.
1991	Ashford and Miller:
	The patient with multiple chemical sensitivities can be discovered by removal from the suspected offending agents and by rechallenge, after an appropriate interval, under strictly controlled environmental conditions. Causality is inferred by the clearing of symptoms with removal from the offending environment and recurrence of symptoms with specific challenge.
1992	American Academy of Environmental Medicine:
	Ecologic illness is a chronic multi-system disorder, usually polysymptomatic, caused by adverse reactions to environmental incitants, modified by individual susceptibility and specific adaptation. The incitants are present in air, water, food, drugs, and our habitat.
1992	National Research Council (NRC), Workshop on Multiple Chemical Sensitivities, Working Group on Research Protocol for Clinical Evaluation:
	Symptoms or signs related to chemical exposures at levels tolerated by the population at large that are distinct from such well recognized hypersensitivity phenomena as IgE-mediated immediate hypersensitivity reactions, contact dermatitis, and hypersensitivity pneumonitis.
	Sensitivity may be expressed as symptoms and signs in one or more organ systems
	Symptoms and signs wax and wane with exposures.
	It is not necessary to identify a chemical exposure associated with the onset of the condition.
	Preexistent or concurrent conditions (e.g., asthma, arthritis, somatization disorder, or depression) should not exclude patients from consideration.
1992	Association of Occupational and Environmental Clinics: Workshop on Multiple Chemical Sensitivity, Working Group on Characterizing Patients:
	A change in health status identified by the patient
	Symptoms triggered regularly by multiple stimuli
	Symptoms experienced for at least 6 months
	A defined set of symptoms reported by patients
	Symptoms that occur in three or more organ systems
	Exclusion of patients with other medical conditions (psychiatric conditions are not considered exclusionary)
1993	Nethercott et al.:
	The symptoms are reproducible with exposure.
	The condition is chronic.
	Low-level exposure results in manifestations of syndrome.
	Symptoms improve or resolve when incitants are removed.
	Responses occur to multiple, chemically unrelated substances.
1995	Kurt:
	The symptoms are "odor-triggered" and "exposure perceived" at very low levels, but are manifest as a multitude of neurobehavioral symptoms that correspond to the accepted definitions of panic disorder.
1996	International Program on Chemical Safety (IPCS):
	An acquired disorder with multiple recurrent symptoms; associated with diverse environmental factors tolerated by the majority of people; not explained by any known medical or psychiatric disorders.

Table 2: Elements Common to Proposed Definitions for MCS since 1985.

Element	Ontario (1985)	Cullen (1987)	Ashford & Miller (1991)	AAEM (1992)	NRC (1992)	AOEC (1992)	Nethercott et al. (1993)	IPCS (1996)
Multiple environmental causes	X	X	X	X		X	X	X
Time (chronicity)	X	X		X	X	X	X	
Multiorgan symptoms	X	X		X	X	X		X
Symptoms at very low levels	X	X			X	X	X	X
Symptoms affected by presence/absence of exposure	X		X		X		X	
Exclusion of other etiologies		X			X	X		X
Symptoms acquired		X				X		X
Demonstrable exposure		X						

The elements most common among the definitions in Table 2 include multiple environmental causes, chronicity, multiorgan symptoms, and symptoms at very low levels of chemical exposure. It is also apparent that Cullen's definition contains the most individual elements. The definition most clinically oriented because of its specificity about symptoms is that of the Association of Occupational and Environmental Clinics (AOEC), a group of primarily university-based clinics that specialize in occupational and environmental medicine. Their definition contains all of Cullen's elements but one (demonstrable exposure).

The California Department of Health Services (CDHS) has proposed the development of a descriptive scale for use in population-based research that could reduce the necessity of prematurely finding one, widely agreed-to case definition. The scale would be based on such factors as the number of substances eliciting responses at low doses, the number of organ systems involved,

symptom severity, symptom chronicity, and initiating events. Each item would be scored individually in multidimensional scale or combined to create a composite monodimensional scale. Subjects' scores would be based on responses to standardized questionnaires (CDHS, 1996). CDHS suggested that this approach would allow the placement of patients along a continuum to create descriptive categories, such as (1) patients with very suggestive scale scores (with or without the presence of confounding medical and psychiatric conditions); (2) respondents with moderately suggestive scores; and (3) respondents with scale scores unlikely to represent MCS. Response scaling allows for maximal use of all respondents, allows for the identification of a subset of respondents who represent the most likely persons to be afflicted, and may prove useful in describing the natural history of the condition. Other subjects can be chosen from along the continuum for a comparison group (see Section II, Epidemiologic Considerations).

Government Interest

Federal and state government interest in MCS has a relatively long history, as documented by Hileman (1991), from which Table 3 is adapted. Selected legal cases are also included in Table 3 because they have occasionally led to action by government agencies. Although not intended to be all-inclusive, the list gives examples of how MCS has been addressed in legal and governmental forums.

Table 3: Selected Legal and Government Actions Relating to MCS, 1979–1996 (Adapted from Hileman, 1991).

1979: U.S. District Court for the District of Hawaii rules MCS disabling and orders the Department of Health, Education, and Welfare to provide Social Security disability benefits to an individual (Slocum vs. Califano).
1984: A California bill to require research on MCS is passed by both houses of state legislature, but is opposed by California Medical Association and vetoed by Gov. Deukmajian.
1985: "Report of the Ad Hoc Committee on Environmental Hypersensitivity Disorders" prepared by the Ontario Ministry of Health, Canada, calls for research on MCS and assistance for MCS patients.
1986: Oregon Court of Appeals orders workers' compensation benefits for furniture store employee on basis of MCS (Robinson vs. Saif Corp.).
1987: National Academy of Sciences (NAS) workshop recommends research on MCS, with assistance from the Institute of Medicine and the National Institutes of Health, to ensure that fundable proposals are developed; NAS Board on Environmental Sciences and Toxicology takes no action on recommendations.
1987: California Court of Appeals awards workers' compensation benefits to employee who was found to have MCS resulting from long-term exposure to polychlorinated biphenyls (Kyles vs. Workers' Compensation Appeals Board).
1988: State of Maryland directs funds for a chemical hypersensitivity study conducted by R. Bascom.
1988: Social Security Administration adds section on MCS to agency's program operations manual for disability determinations.
1989: Ashford and Miller prepare a report on MCS for the New Jersey State Department of Health.
1989: Indoor Air Quality Act introduced in Senate addresses MCS.
1989: Ohio Court of Appeals reinstates an order of the Ohio Civil Rights Commission finding unlawful employment discrimination for dismissal of an employee with MCS (Kent State University vs. Ohio Civil Rights Commission).
1990: Department of National Health and Welfare in Canada convenes a workshop on MCS to develop priorities for research into MCS and to identify the health needs of MCS patients; report is issued in January 1991.
1990: Pennsylvania Human Relations Commission orders a landlord of an MCS patient to take measures to accommodate her, including reduction in the use of pesticides (Atkinson vs. Lincoln Realty).
1990: Office of Technology Assessment declines to include the issue of MCS in its report on immunotoxicology research needs.
1991: At request of EPA, Division of Indoor Air, NAS organizes a workshop of invited experts on MCS; research recommendations are developed.
1991: The Association of Occupational and Environmental Clinics (AOEC), under the sponsorship of ATSDR, organizes a meeting to focus primarily on the clinical aspects of the condition.
1992: Department of Housing and Urban Development recognizes MCS as a disability requiring reasonable accommodations under the Fair Housing Act Amendments and the Rehabilitation Act of 1973.
1992: As a part of the Fiscal Year 1993 budget process, Congress mandates ATSDR to utilize $250,000 for "[c]hemical sensitivity/low-level chemical and environmental exposure workshops."
1993: ATSDR, addressing a Congressional mandate, convenes a panel of experts to offer guidance on initiatives it should undertake, given the current state of knowledge and the resources available.
1994: ATSDR convenes a national meeting in Baltimore to consider the neurobiologic aspects of chemical sensitivity.
1995: State of Washington designates $1.5 million research fund for chemically related illness.
1996: A workshop organized by the International Program on Chemical Safety meets in Berlin; majority of participants suggest "idiopathic environmental intolerances" (IEI) to replace the term "MCS."

In addition to the items in Table 3, there have been a number of other state actions. California, Louisiana, Minnesota, Ohio, Oregon, and Pennsylvania have ruled in favor of MCS claimants in workers' compensation cases, but this situation can and does change with shifts of policy and personnel in the states. Gots (1995) has stated that the number of MCS claims continues to rise. New Hampshire has a workers' compensation act that recognizes the condition; in addition, several state court decisions in California, Ohio, and other jurisdictions have found that MCS conditions qualify as handicaps for purposes of state employment discrimination statutes (Lieberman et al., 1995).

Florida was the first state to pass legislation creating a pesticide notification registry for persons claiming chemically related illness. Typically, these registries require that notice of impending pesticide application to abutting property be given to persons listed on the registry. Some registries also require notification for painting, repair, and construction. A physician's certification of sensitivity to chemicals is usually required before a person can be enrolled in a registry. Currently, 10 states (Colorado, Connecticut, Florida, Louisiana, Maryland, Michigan, Pennsylvania, Washington, West Virginia, and Wisconsin) have created notification registries through legislation. There have also been successful efforts to reduce the medical requirements needed for persons to be placed on state registries. Colorado, for example, may allow admittance to its pesticide sensitivity registry through a document signed by licensed physicians regardless of the geographic areas in which they practice medicine (Langley, 1995).

Perhaps the most significant MCS legislation passed by a state was enacted by Washington State in 1994. Several medical centers were funded to diagnose and treat chemically related illness or porphyrinopathy (Langley, 1995). In addition, Washington State announced in 1996 the funding of six projects on chemically related illness totaling $1.4 million. The projects included research on the validity of immune and lymphocyte tests in MCS patients and controls, the relationship of brain function to MCS, and the development of objective tests for evaluation of MCS patients. Related projects included investigation of (1) the relationship between low levels of volatile organic compounds and functional/inflammatory changes in the lungs or sinuses and (2) the potential health effects of exposure to the dusts of various tree species and to certain metals (Washington State, 1996b).

II. Epidemiologic Considerations

Investigators gathering data about MCS often develop their own case definitions and, in almost all investigations, they rely on symptoms reported by the study participants. Likewise, data concerning the prevalence of MCS are limited and must be reviewed in light of any potential reporting errors and other errors that lead to misclassification, selection, and other related biases. Some investigators express the prevalence of self-reported, physician-diagnosed MCS, whereas other investigators report the prevalence of persons who report feeling ill from exposure to chemicals, or being sensitive to chemicals, but do not profess to have MCS.

As described in the following sections, epidemiologic investigations of MCS can be grouped into two kinds of study, depending on the populations comprising the studies. Epidemiologic studies of the prevalence of MCS in the general population constitute one kind of study. The other kind of study uses methods from descriptive epidemiology and has focused on groups who have indicated their hypersensitivity to chemicals.

Prevalence Studies

On the basis of conversations with clinicians, Mooser (1987) suggested that 2–10 percent of persons in the general population have substantive disruption of their lives because of MCS. Cullen et al. (1992) later contested that this range was too high.

The U.S. Environmental Protection Agency (EPA) reported that about one-third of persons working in sealed buildings felt especially sensitive to one or more common chemical exposures (USEPA, 1991).

Bell and colleagues investigated the prevalence of chemical sensitivity in two groups of subjects, young adult college students and elderly persons. They found that 15 percent of a sample of college students reported feeling moderately or severely ill after exposure to at least four of five common substances (i.e., pesticides, paint, perfume, car exhaust, and new carpet) (Bell et al., 1993a). Twenty-two percent of college students (Bell et al., 1993b) reported feeling moderately or severely ill after exposure to at least three of the five substances. The same investigators (Bell et al., 1996a) found that the proportion of college students who report feeling ill or sensitive to environmental

chemicals depends on how they are queried about such symptoms. In this study, 9.7 percent reported illness, sometimes or more often, from 6 to 10 environmental chemicals (new carpet, newsprint, disinfectant, paint, natural gas, perfume, tar, pesticide, car exhaust, tobacco smoke). Twenty-eight percent considered themselves to be "especially sensitive to certain chemicals." Only 0.2 percent reported physician-diagnosed MCS.

Bell et al. (1993c) reported that 17 percent of a group of retired elderly persons participating in a longitudinal study of osteoporosis reported feeling moderately or severely ill after exposure to at least four of five common substances (pesticides, paint, perfume, car exhaust, and new carpet). In subsequent reports 34 percent of the same study group of elderly persons (Bell et al., 1994) and 37 percent of elderly veterans (Bell et al., 1997a) considered themselves "especially sensitive to certain chemicals." Overall, 4 percent of the participants in the study of community elderly (Bell et al., 1994) reported physician-diagnosed chemical sensitivity.

Baldwin et al. (1997) found that 22.7 percent of a subset of urban employed persons participating in a study investigating relationships between indoor and outdoor air contaminants on respiratory health reported feeling moderately or severely ill after exposure to at least 3 of 5 substances (pesticides, paint, perfume, car exhaust, and new carpet) .

Meggs et al. (1996) conducted a random telephone survey to determine the self-reported prevalence of allergy and sensitivity to chemicals in a rural population in North Carolina. The survey defined allergy as "becoming sick from exposure to natural things (e.g., pollen, dust, grass, trees, cats, dogs, mold, feathers, foods)." Sensitivity to chemicals was defined as "becoming sick after smelling chemical odors (e.g., perfume, pesticides, fresh paint, cigarette smoke, new carpets, car exhaust)." Of 1,027 persons who participated in the survey, 35 percent reported allergies and 33 percent reported sensitivity to chemicals. Thirty-five percent of those who were sensitive to chemicals reported that symptoms occurred at least once each week. Symptoms of sensitivity to chemicals that occurred daily were reported by 3.9 percent of the total population; allergic symptoms that occurred daily were reported by 5.3 percent of the total population. The investigators cautioned, "This study was not designed to determine the prevalence of specific syndromes for which chemical sensitivity has been described (e.g., asthma and rhinitis, solvent-exposed workers, office workers in 'sick buildings', people poisoned by organophosphate pesticides, individuals with the MCS syndrome). These results, therefore, cannot be used to draw conclusions about the prevalence of these specific

conditions."

In 1993, the California Department of Health Services (CDHS) received a MCS-relevant grant from ATSDR to assemble a multidisciplinary panel of experts. Their task was to advise the agency on development of questionnaires, a battery of medical examinations, laboratory tests, and recommendations for epidemiologic study designs for implementation in the event of a community chemical spill. Four questionnaires were developed: (1) a set of 12 general population-screening questions, (2) a set of household-screening questions for use in a post-spill situation, (3) a "long-form" questionnaire for in-depth population-based research, and (4) a follow-up questionnaire. The 12 general population-screening questions were pilot tested by being included on the 1995 California Behavioral Risk Factors Surveillance (BRFS) telephone survey of 4,000 randomly selected California residents. According to Kreutzer and Neutra, the results showed that 16 percent of survey participants reported sensitivities to everyday chemicals, and 6 percent claimed to have been diagnosed with multiple chemical sensitivities by a doctor (personal communication, 1996). CDHS has developed a plan to further evaluate these incidence and prevalence data through in-depth interviews with the BRFS survey respondents who reported chemical sensitivities and a smaller number of respondents not reporting sensitivities.

In summary, studies report the prevalence of feeling ill after exposure to chemicals or being sensitive to chemicals, but not necessarily having MCS, ranges from 15 to 37 percent. However, because the relationship between cacosmia (i.e., a heightened sensitivity to odors) and the later development of MCS is unknown, the relevance of most of these studies to MCS is unclear. Only three studies have reported the prevalence of self-reported physician-diagnosed MCS. The prevalence of self-reported physician-diagnosed MCS ranges from published values of 0.2 percent in college students (Bell et al., 1996a) to 4.0 percent in elderly persons (Bell et al., 1994) and an unpublished value of 6 percent among randomly selected California residents (Kreutzer and Neutra, personal communication, 1996).

Descriptive Epidemiologic Studies

In 1989, the National Foundation for the Chemically Hypersensitive, an MCS patients advocacy group, surveyed 6,800 persons claiming to be hypersensitive and found that 80 percent knew "when, where, with what, and how they were made ill." Pesticides were described as the initiating factor by 60 percent of this group (48 percent of all participants) (cited in Ashford and Miller, 1991).

However, these results may not be applicable to the overall U.S. population.

Kipen et al. (1995) modified a questionnaire designed to identify environmental exposures in patients' living situations and tested it for use in population studies to assess the presence or absence of chemical sensitivity. The questionnaire asked whether exposure to various substances caused symptoms (defined as some discomfort or bothersome change). The questionnaire was administered (1) to 41 patients receiving health care at a general medicine clinic (medical clinic patients) and (2) to persons visiting an environmental and occupational health center, including 436 persons referred for routine prescribed surveillance or baseline examinations because of their employment (surveillance patients), 39 persons who met the investigators' criteria for MCS (MCS patients), 43 persons with a diagnosis of asthma or airway hyperreactivity but not MCS (occupational clinic patients with asthma), and 137 patients with a wide range of occupational and environmental health diagnoses (occupational clinic referrals). The MCS patients reported that significantly more substances elicited symptoms than did other groups. Patients with asthma reported significantly more substances elicited symptoms than the surveillance, occupational medicine referral, and medical clinic patient groups. Four percent of surveillance patients, 15 percent of occupational clinic referrals, 20 percent of medical clinic patients, 54 percent of occupational clinic patients with asthma, and 69 percent of MCS patients were identified as reporting symptoms with exposure to 23 or more substances. Although the investigators did not know if some of the patients in the medical clinic and surveillance groups would have qualified as having MCS, they point out that this would have improved both specificity and predictive values.

In a case series of 100 consecutive patients admitted to an environmental ecology (primarily MCS) unit at a Texas hospital, the median age of the patients was 40 years; 56 percent of these patients began having their symptoms before 30 years of age, 77 percent were female, and more than half had 4 years of college (as cited in Spyker, 1995). A self-assessment survey of initiating factors was also conducted. Twelve percent of the study population considered the initiating factor to have been an occupational exposure, and 11 percent, a new environment (i.e., home, job, or college); 58 percent could not identify an initiating factor (as cited in Spyker, 1995). Rea (1995) recently expanded this case series to a review of 30,000 patients seen over a 20-year period. In this case series, females outnumbered males at a ratio of 7:1. The predominant age range for developing chemical sensitivity was 30–50 years, although MCS had been diagnosed at Rea's clinic in both infants and older patients. Rea also noted that, in this case series, males had a higher death rate than

females. He also stated that although the rate of end organ failure was the same for males and females, the organs predominantly affected differed by sex. No data were presented to support these findings (Rea, 1995).

Miller and Mitzel (1995) reviewed the history of symptoms in 112 persons already diagnosed as having MCS: 83 percent had onset of symptoms after age 30 years and had a predominance of cognitive symptoms; 81 percent had been working full time when exposed, but only 12 percent were fully employed at the time of the survey. A majority stated that they had quit their jobs or changed jobs or careers because of their illness. About 40 percent had consulted 10 or more medical practitioners.

To evaluate workplace conditions possibly associated with MCS, Lax and Henneberger (1995) investigated MCS patients examined by an occupational health clinic. Computerized records of 605 patients were reviewed to identify those individuals who met a MCS case definition similar to the Cullen definition. Thirty-nine of the 605 patients (6.4 percent) met the criteria for MCS diagnosis; four were excluded because they had non-occupational-related onsets of MCS. The remaining 35 MCS patients were compared with 557 patients who had no indication of MCS. The 35 MCS patients were interviewed by telephone to survey health status and exposure histories. Findings showed 80 percent of the MCS patients and only 25 percent of the other patients were female. Also, the two groups of patients were very different with respect to the industries in which they were employed. For example, 54 percent of the non-MCS patients worked in industries considered to have a greater potential for hazardous exposures than other occupational settings; only 26 percent of the MCS patients were employed in the more hazardous industries. Notwithstanding the small number of MCS patients and limitations in exposure history surveys, Lax and Henneberger concluded, "Commonalities in exposure and symptoms suggest that Multiple Chemical Sensitivities represents a distinct diagnostic category."

Davidoff and Keyl (1996) compared four diverse MCS study groups with one another and with a matched general population group with respect to self-reported health and mental health history and status variables. Three of the MCS groups were similar in that they met the investigators' criteria for multiple chemical sensitivities syndrome, but they were unique in having developed this syndrome in response to different sensitizing exposures (i.e., organic solvents, organophosphate pesticides, and sick building syndrome). The fourth MCS group consisted of 10 workers from a

potato processing plant who had developed conditions that resembled MCS after they were exposed by accident to both chlorine dioxide gas and chloroform. With respect to health status, ratings of "fair" or "poor" health and changes in health were more characteristic of the four MCS groups than for the general population group. The study suggested that the MCS groups were not significantly different from one another in health and illness status. While members of all groups reported changed tolerances to substances, MCS group members were more likely to attribute illness to chemical exposures on a daily basis and to place recovery from the ill effects at more than 12 hours after exposure. Frequency of members reporting three or more chronic childhood health conditions, which the investigators suggested was evidence of longstanding somatic complaints or complaints of sickliness in childhood, was seen relatively often in the MCS groups, but was observed rarely in the general population group. Negative affect, a psychiatric index score used in this study, was consistently higher in MCS groups than in the general population group. The investigators recognized possible limitations of the study, such as group selection methods.

Most studies show that a preponderance of patients with MCS are females, 30–50 years of age, with an above-average socioeconomic status (Cullen, 1992). Sparks et al. (1994) cited four studies documenting a preponderance of females reporting MCS symptoms, and other investigators also have published a similar finding. The reasons for this apparent preponderance are unknown.

A higher prevalence of a variety of medical conditions has been observed among cacosmic persons identified by the Cacosmia Screening Index and the relatives of these persons (Bell et al., 1994; Bell et al., 1995b; Bell et al., 1996; Baldwin et al., 1997). However, only one study (Bell et al., 1995a) compared personal and family medical and psychiatric histories of persons who have MCS with a control group. In this study, healthy cacosmics and healthy noncacosmics served as comparison groups. The prevalence was highest in the MCS group for self-reported physician-diagnosed rhinitis, chronic bronchitis, migraine headache, irritable bowel, arthritis, chronic fatigue syndrome (CFS), hypoadrenocortical function, candidiasis, ovarian cysts, menstrual cycle irregularities, painful menses, chronic pelvic pain, heavy menstrual bleeding, depression, anxiety, and panic disorder. The MCS group also reported the highest prevalence of rhinitis and diabetes mellitus among family members. The prevalence of family histories of depression, anxiety, panic disorder, and substance abuse were not significantly different between the groups.

Summary Comments on Epidemiology

A particularly important question about MCS is its prevalence in the general population. Only three studies have reported the prevalence of self-reported physician-diagnosed MCS. The prevalence of self-reported physician-diagnosed MCS ranges from published values of 0.2 percent in college students (Bell et al., 1996a) to 4.0 percent in elderly persons (Bell et al., 1994) and an unpublished value of 6 percent among randomly selected California residents (Kreutzer and Neutra, personal communication, 1996).

A review of the current knowledge about epidemiology of MCS reveals that the only consensus descriptive or demographic data are the age range and sex of MCS patients. In addition, it is difficult to compare the results of studies on MCS conducted by different investigators. There is no consensus definition of MCS among the investigators, and they usually do not provide detailed descriptions of the methods used to document symptom complaints, identify environmental triggers that produced symptoms, or specify criteria used for inclusion or exclusion of subjects. The use of standardized questionnaires is one way to improve comparison of results across MCS investigations (CDHS, 1996). Other ways to improve the design and conduct of epidemiologic studies are discussed in Section IV.

561 ## III. Theories of Causation and Mechanisms

562 ### Introduction

563 The proposed theories of causation of MCS can only be summarized in this report. Although these
564 theories can be grouped into three broad categories (immunologic, neurologic, and psychological),
565 there are many variations. Some theories are interrelated, and each theory is still being considered
566 and debated within the scientific community. For example, Miller et al. (1997) proposed a theory
567 of "toxicant-induced loss of tolerance" (TILT), which suggests that acute or chronic chemical
568 exposures might cause certain susceptible persons to lose their tolerance for previously tolerated
569 chemicals, drugs, and foods. Subsequently, even minute quantities of these and other substances may
570 trigger symptoms. They argue that TILT may prove to be a new theory of disease causation parallel
571 to the germ, immune, and cancer theories.

572 Discussions regarding the mechanisms of MCS can be divided into two distinct categories. Some
573 persons assert that MCS symptoms are psychologically based or have strong psychological
574 components. Others who accept a physiological basis for MCS may concur that psychological
575 factors are present, but contend that they are only a component of the condition or are the natural
576 result of coping with an intractable chronic condition.

577 The following sections summarize key literature on immune system, neurologic, and psychological
578 mechanisms postulated to be associated with MCS.

579 ### Immune Mechanisms

580 Disorders of the immune system have been suggested as causing or contributing to MCS (Rea et al.,
581 1992; Levin and Byers, 1987; Thrasher et al., 1990; Heuser et al., 1992; Ross, 1992; Levin and
582 Byers, 1992). Some practitioners employ tests for immune sensitization and/or laboratory
583 determinations of immune parameters in diagnosing MCS, and some use therapeutic regimens
584 directed at correcting putative immune deficiencies (Rea et al., 1992; Heuser et al., 1992; Ross 1992;
585 Levin and Byers, 1992). However, these investigators generally agree that MCS differs from
586 disorders known to be associated with overt immunopathology (i.e., allergies, immune deficiencies,
587 and autoimmune diseases) and suggest that MCS is not mediated solely by known immune
588 mechanisms (Ziem, 1992). Instead, MCS is argued to be associated with a more general form of

589 "immune dysregulation" which leads to the MCS symptom complex, perhaps through interaction
590 of immune mediators with the neuroendocrine systems (Meggs, 1992; Levin and Byers, 1992).

591 The theories and reports of immune involvement in MCS presented by some environmental
592 medicine practitioners have not been accepted by most physicians and researchers (Terr, 1987;
593 Albright and Goldstein, 1992), but some do acknowledge that allergic or immunotoxicologic
594 reactions could be contributing factors in at least a subset of MCS patients (Selner and
595 Staudenmayer, 1992; Albright and Goldstein, 1992; Meggs, 1992). Because immune responsiveness
596 and inflammation are closely related, hypotheses relating inflammation to MCS (which are discussed
597 in the next section) are likely to overlap with immunologic considerations (Meggs, 1992).

598 Evidence for or against immune involvement in MCS depends to some extent on laboratory
599 measurements of certain immune biomarkers (defined by the National Research Council [NRC]
600 [1987] as "[i]ndicators of events in biological systems or samples"). Some studies have reported that
601 results of immune biomarkers lie outside "normal" ranges in many MCS patients (Heuser et al.,
602 1992; reviewed in Meggs, 1992). Immune abnormalities reported to be associated with MCS include
603 alterations in the distribution of peripheral blood lymphocyte subsets, increases in the proportion
604 of activated T-cells in circulation, and abnormal serum antibodies to tissue antigens and
605 chemical-protein conjugates (Rea et al., 1992; Thrasher et al., 1990; Heuser et al., 1992; Levin and
606 Byers, 1992). In contrast, studies conducted by other researchers have not detected abnormal
607 immune test results in MCS patients (Terr 1986; Simon et al., 1993).

608 The role of the immune system in MCS is difficult to assess from many of the published reports
609 because the laboratory methods are inadequately documented or, in some cases, clearly deficient.
610 Results reported for lymphocyte phenotypes illustrate these methodologic concerns. For example,
611 Levin and Byers (1987) cited results originally reported in court records but gave no methodologic
612 information. Similarly, an article by Terr (1986), provides no description of laboratory methods.
613 Another example is the use of an inadequate method, peripheral blood lymphocyte phenotypes
614 determined by manual fluorescent microscopy on separated cells, to assess the role of the immune
615 system in MCS (Thrasher et al., 1990; Simon et al., 1993). This technique is considered to be
616 unacceptable for clinical use (Kidd and Vogt, 1989; CDC, 1992). Comparable methodologic
617 uncertainties attend reports on immune tests for autoantibodies, antibodies to chemical-protein
618 conjugates, and cellular function assays in MCS patients (Vogt 1991; Vogt and Margolick , 1994).

Fully controlled studies with appropriate quality assurance are needed to verify the suggested changes in immune system markers postulated to be associated with MCS.

In addition to limitations in laboratory analyses, another major difficulty with interpreting data on immune functions and MCS is the lack of sound epidemiologic methods in most of the published reports, which are limited to individual cases or small numbers of individuals identified in clinical settings. While such reports have value in suggesting directions for rigorous investigations with sound study design, they must be interpreted cautiously because they do not account for the numerous confounding variables (including age, sex, smoking, diurnal and seasonal variation, and stress) that can influence immune parameters (Vineis et al., 1993).

The importance of both laboratory methods and epidemiologic design has been underscored by one particular study of MCS and immunologic tests (Simon et al., 1993). The study used careful epidemiologic design to determine the usefulness of certain immunologic tests in discriminating MCS patients from matched controls. The results showed clearly that the immunologic tests, as selected and performed by a laboratory specializing in tests for MCS, were of no use for identifying MCS patients. Subsequent to the publication of this study, one of its investigators, Simon, released unpublished results from 10 sets of split (i.e., duplicate) samples (20 specimens), to which the specialty laboratory had been blinded, showing that results across samples had not been replicated (Friedman et al., 1994).

The sound epidemiologic design of this study was important for raising questions about the reliability of results from the specialty laboratory and reports previously published by the laboratory (Thrasher et al., 1990). Moreover, because the same laboratory was used by at least one physician who claimed to have found immunologic tests useful for diagnosing MCS (Friedman et al, 1994), the results of the Simon et al. (1993) study cast doubt on some accounts that suggest immune system involvement in MCS. However, because of the laboratory deficiency, the study provides inadequate information about immune effects in MCS patients.

Clarification of the role of the immune system in MCS may be forthcoming from an ongoing multicenter study that is comparing results on a comprehensive panel of immunologic biomarkers between MCS patients and matched controls using rigorous inter-laboratory quality assurance

(personal communication, Joseph B. Margolick, Johns Hopkins University).

Inflammation

Inflammation has been suggested as being causally related to MCS as a result of the initiation of mediators released from cell membranes by the action of free radicals produced from toxic chemical exposures (Sparks et al., 1994). Bascom (1992) has suggested that exposure to low-level irritants may result in chronic respiratory health effects and that "[d]ifferential susceptibility exists to illnesses resulting from chronic exposure to irritant mixtures." She suggests this occurs through several mechanisms, primarily induction of inflammation through irritation of the upper airway epithelium.

The role of respiratory tract inflammation in MCS has also been hypothesized to resemble the changes seen in other conditions that include hyperreactivity of the airways. It has been suggested that a single acute, high-dose induction exposure to a chemical is followed by a chronic intolerance to low levels of chemicals. This two-stage process has been observed in reactive airways dysfunction syndrome, in which a high-dose exposure to airway irritants is followed by chronic asthma with bronchial hyperactivity (Brooks et al., 1985). Meggs has theorized that patients who develop rhinitis after a single high-dose exposure can be said to have reactive upper-airways dysfunction syndrome (Meggs, 1995). He suggests that chemical sensitivity may be a symptom of airway inflammation. In support of this hypothesis, Meggs gives several examples of studies where chemical sensitivity was associated with upper airway disease for which the examined health outcomes did not require rhinolaryngoscopic examinations (e.g., Doty et al., 1988; Chester, 1991). Fiber-optic rhinoscopy has been used to detect nasal inflammation in a chemically sensitive population, and nasal biopsies have indicated chronic inflammation and a cobblestone appearance of the pharynx and tongue accompanied by mucosal injection (Meggs and Cleveland, 1993).

Meggs (1995) reported airway inflammation that he noted on rhinolaryngoscopic examinations; he hypothesized that inflammation in the airways can produce many of the extra-airway symptoms seen in MCS. He argued that patients with allergies have extra-airway symptoms such as nausea, fatigue, mental confusion, and myalgia at sites other than the site of inoculation with antigen. He speculated that the mechanism by which chemicals cause airway inflammation is a chemical interaction with chemoreceptors on sensory nerves, leading to release of substance P and other mediators of neurogenic inflammation. Leznoff, however, reported that five patients he examined who

complained of throat-related symptoms (choking, cough, dysphonia, and "swollen glands") following challenge with a chemical showed no visible changes in the throat or larynx using fiber-optic laryngoscopy and no change in recorded phonograms (Leznoff, 1992). It should be noted that in neither of the two previous studies where the investigators were blinded (i.e., unaware) to the MCS status of the patients.

In studies that have been useful in elucidating inflammogenic pathways, inflammatory mediators (including cytokines and neuropeptides) have been quantified in serum and in nasal biopsies, scrapings, and washings of persons with well-defined allergic and nonallergic inflammatory reactions (Straight and Vogt, 1997). There is no convincing evidence that such mediators are involved with MCS (Salvaggio, 1992), although the hypothesis has not been adequately tested. The analytical methods for measuring these mediators require close attention, because many of the assays yield highly variable results between different sources and even between different reagent lots from the same source.

Neurologic Mechanisms Including Altered Sense of Smell

Of the neurophysiologic models that have been advanced to explain MCS-related clinical phenomena and to provide possible mechanisms for the condition, the olfactory-limbic and neural sensitization model developed and refined by Bell and colleagues is the one most completely explicated (Bell et al., 1992; Sparks et al., 1994). In a description of this model, Bell et al. (1997b) proposed that neural stimulation is the underlying mechanism for the disorder. Neural stimulation is defined as the "[p]rogressive amplification of responsivity by the passage of time and repeated, intermittent exposures" and can be initiated by a single exposure to a chemical or by multiple low-level exposures. Several forms of sensitization are proposed, including "limbic kindling," a phenomenon described in animal research in which exposures to excitants, such as electricity or chemicals, result in abnormal electrical activity in the brain and seizures or seizure-like phenomena. Other forms of sensitization include time-dependent sensitization of neurochemical, immunologic, endocrinologic, and behavioral responses. According to Bell's model, these forms of sensitization directly involve limbic and mesolimbic systems in the brain. Because these brain systems include structures that are known to be associated with emotion and cognition, Bell concludes that the cognitive and mood symptoms associated with MCS are related to the involvement of these brain regions through sensitization. She feels that sensitization is distinct from other possible mechanisms associated with MCS symptomatology (e.g., conditioning and habituation), but suggests that these

distinct mechanisms might be integrated to better explain MCS.

To test their model of MCS, Bell and colleagues have conducted a number of studies comparing persons who are chemically intolerant and chemically tolerant (based on the cacosmia screening index). In studies of college students, Bell has tied the phenomenon of chemical intolerance to limbic system function through demonstration of associations between higher reports of psychological distress and drug use (Bell et al., 1996a) and higher rates of personal histories of anxiety and depression and family histories of substance abuse (Bell et al., 1995b) among students who report chemical intolerance in comparison with those without such intolerance. In the latter study, she also reported that the chemically intolerant students scored higher on a measure of "limbic system symptoms" than did the chemically tolerant students. As support of the limbic system hypothesis, Bell and colleagues have also reported lower scores on a memory test among chemically intolerant persons in a sample of Veterans Administration patients (Bell et al., 1997a) and slowed reaction times on a divided attention task performed by chemically intolerant retired adults (Bell et al., 1996b). In a series of studies, Bell et al. (1996c, 1996d, 1997d) reported changes in endorphin levels, blood pressure, and wakefulness in chemically intolerant persons relative to controls. All of these studies represent attempts to explore the hypothesized model. It should be noted that the experiments have been carried out primarily among persons who had not received a diagnosis of MCS.

Animal models of sensitization have been proposed and initiated (Sorg et al., 1994; Sorg, 1995; Bell et al., 1997c). Gilbert (1995) reported that rats with chronic, low-dose exposure to lindane developed electrical changes in the brain and seizure-like symptoms, while those with a single-dose exposure did not. He tied these results to the concept of chemical kindling. Animal models have also been used to test hypotheses that responsivity to chemicals might have a genetic component (Wang et al., 1993). In addition, the use of a specific breed of rats (Flinders Sensitive Line rats) that are highly sensitive to the organophosphate diisopropylfluorophosphate and which have increased cholinergic receptors and behavioral changes resembling those seen in human depression has been suggested for studies in animal models of MCS (Overstreet et al., 1996).

In a study of odor responsivity among persons diagnosed with MCS, Fiedler et al. (1995) tested 31 subjects to assess odor detection thresholds to rose-scented alcohol and an unpleasant-smelling pyradine; no differences were found between the MCS subjects, controls, and asthma patients.

738 Quantitative electroencephalography (EEG), brain electrical activity mapping (BEAM), positron
739 emission tomography (PET), and single photon emission computed tomography (SPECT) have been
740 used as neurologic correlates of MCS. Mayberg (1994) reviewed the studies that used these methods
741 and concluded that, although patterns seen in some studies have shown abnormalities that might be
742 related to MCS (particularly with SPECT), these studies are deficient in standardization of
743 techniques, replication of results using testable hypotheses, and use of appropriate control groups.

744 **Psychological Mechanisms**

745 Psychiatric factors have been seen as the *cause* of MCS, an *effect* of having MCS, a *predisposing*
746 *factor* in the development of MCS, and a *co-morbid* occurrence with MCS. Some investigators
747 believe that MCS is a somatoform reaction (i.e., physical symptoms not explained by objective
748 clinical findings), if not a frank psychiatric condition. For example, one investigator believes the
749 symptom complex of MCS resembles the DSM-III-R description for panic disorder (Kurt, 1995),
750 and others have suggested that MCS is an "odor-triggered panic attack" (Shusterman and Dager,
751 1991).

752 Black et al. (1990) conducted a study on the emotional profile of persons identified as having
753 "environmental illness." Persons who were included had illnesses diagnosed as chronic yeast
754 disease, environmental allergy syndrome, 20th century disease, and the multiple chemical
755 hypersensitivity syndrome. No physical or laboratory examinations were included. Significantly
756 more study subjects than controls met lifetime criteria for a major mental disorder, suggesting that
757 patients with a diagnosis of environmental illness may have one or more commonly recognized
758 psychiatric disorders that could explain some or all of their symptoms. Psychiatric diagnoses were
759 recommended for consideration as an explanation for patients with multiple ill-defined symptoms
760 in the absence of clinical or laboratory findings. This suggestion was supported by an earlier study
761 (Stewart and Raskin, 1985) of patients with "20th century disease." Another study (Simon et al.,
762 1993) compared 41 patients who had chemical sensitivity with 34 control patients who had chronic
763 musculoskeletal injuries to examine the role of psychological and other factors in MCS.
764 Psychological evaluation included standardized measures of anxiety, depression, and somatization.
765 Patients with chemical sensitivity reported a greater prevalence of current anxiety or depressive
766 disorder, but this difference did not appear to precede the onset of chemical sensitivity. The
767 investigators concluded that psychological symptoms, while not necessarily a cause, are a central
768 component of chemical sensitivity. Davidoff and Fogarty (1994) have pointed out methodologic

problems, such as patient selection, in these and other reports.

Fiedler and colleagues have examined neuropsychological test performance as a marker of central nervous system (CNS) dysfunction in patients in whom MCS has been diagnosed or who have related problems. In 1992, Fiedler et al. summarized data on 11 patients who met Cullen's criteria for diagnosis of MCS. On the basis of these data, the investigators concluded that there were neuropsychological findings suggestive of CNS involvement in MCS. This conclusion was questioned in a later study (Fiedler et al., 1996). In this study, Fiedler and colleagues compared neuropsychological and psychiatric function among MCS patients who met and those who did not meet Cullen's criteria of MCS (labeled MCS and CS, respectively), patients who had chronic fatigue syndrome (CFS), and healthy controls. Standardized measures of psychiatric and neuropsychological function did not distinguish the MCS and CS groups from the CFS group. The prevalence of current Axis I Psychiatric Diagnosis was higher in the MCS, CS, and CFS groups than in controls. Seventy-four percent of MCS, 38 percent of CS, and 61 percent of CFS patients did not meet criteria for any current Axis I Psychiatric Diagnosis. Neuropsychological test results did not account for the level of impairment implied by the patients' symptom reports.

It has been suggested that MCS is an example of a conditioned response (Siegel and Kreutzer, 1997). In classical conditioning, a neutral conditioned stimulus is paired with an unconditioned stimulus. The unconditioned stimulus reflexively elicits some response, termed the unconditioned response. Initially, the conditioned stimulus does not evoke a response. However, as a result of conditioned stimulus-unconditioned stimulus pairings, the conditioned stimulus becomes associated with the unconditioned stimulus. As a result, the previously neutral stimulus elicits a new response, termed the conditioned response. Once established, generalization may occur during which the conditioned response is elicited by stimuli other than the conditioned stimulus. Typically, the greater the similarity between the novel stimulus and the conditioned stimulus used during acquisition, the greater the strength of the generalized conditioned response. Davidoff (1992) examined three models of MCS, including the classical conditioning model. She listed predictions derived from this model, including those that incitants will have somewhat similar odors and that responses will be "stereotyped and reflex-like" and will occur predictably with certain odors. This model also does not require prior psychopathology, because emotional responses can be reflexively induced. Davidoff listed data consistent with the classical conditioning model, including reports of the absence of a psychiatric history predating the condition and reports that odor awareness is often

800 salient in MCS. She also listed data inconsistent with the classical conditioning model, including
801 MCS patients' reporting that odors and response patterns to incitants vary (Davidoff, 1992).

802 A 1993 exposure chamber study that was designed to investigate odor thresholds and the ability of
803 MCS patients to determine the presence of chemicals included double-blind provocation challenges
804 to 20 patients (Staudenmayer et al., 1993). The investigators used an olfactory masker and a variety
805 of chemicals (i.e., one chemical per patient); each patient received 5–10 challenges. All patients
806 believed that they were reactive or hypersensitive to low-level exposure to multiple chemicals. Clean
807 air challenges that contained the olfactory masker were used as placebo controls. As a group, the
808 patients did not show a "reliable response pattern across a series of challenges." The patients as a
809 group showed 33.3 percent sensitivity, 64.7 percent specificity, and 52.4 percent efficiency in
810 responding to stressors. The investigators concluded that such testing helps differentiate toxicologic
811 mechanisms from psychological mechanisms such as stress psychophysiology and learned
812 sensitivity. However, the results of this study may have been influenced by the choice of placebos
813 used in the experiment, the use of masking, and the outcome measures that were used. In an earlier
814 report, the same investigators suggested that, in any environmentally related case, an evaluation
815 should be made of psychological motivation and evidence of psychological symptoms, including
816 repressed childhood trauma (Selner and Staudenmayer, 1992).

817 In summary, the suggestion that psychiatric disorders are the basis of MCS has complicated
818 communication between those who believe that, if present, psychiatric symptoms are a secondary
819 accompaniment to a chronic disease process and those who believe that MCS is primarily the
820 symptomatic manifestation of a psychiatric disorder. The thread of this debate runs throughout the
821 discussion of MCS. It continues despite recent evidence that many disorders and syndromes that are
822 considered to be psychiatric (e.g., panic disorder and post-traumatic stress disorder) are
823 accompanied by measurable changes in brain function as assessed by techniques such as functional
824 magnetic resonance imaging and single photon emission computed tomography (Dager and Steen,
825 1992).

826 Although causal psychological mechanisms in MCS remain uncertain, the data suggest that
827 psychological factors should be carefully evaluated in the diagnosis and treatment of patients who
828 have MCS. The workgroup finds the need for carefully designed studies to evaluate both the
829 primary and secondary psychological factors in MCS.

Other Syndromes

Sick Building Syndrome

Although not discussed in detail in this report, the syndrome known as Sick Building Syndrome (SBS) has been linked to MCS as an initiating factor. Persons with SBS experience symptoms that include eye, nose, and throat irritation; headaches; cough; difficult breathing; fatigue; dizziness; and difficulty in concentrating. These symptoms are temporally related to being in a particular building. The cause of SBS is unknown, but it is often thought to result from poor building ventilation causing a buildup of vapors from sources that include building materials, furnishings, and office equipment. SBS has also been linked to contamination of indoor spaces or ventilation systems by biologic organisms. Occasionally, some persons with SBS report that they later develop MCS. One published study describes the clinical followup of 20 persons whose work-related illnesses were considered related to a "sick building" (Welch and Sokas, 1992). Over time, three of the 20 persons had ongoing symptoms consistent with Cullen's definition of MCS.

Porphyria

Several MCS patients have been reported with neurologic and/or cutaneous symptoms suggestive of porphyrin disorders (Ziem and McTamney, 1995). These patients reported symptoms such as "dark brown or red urine," skin sensitivity to sunlight exposure, and sharp abdominal pain. Porphyrin disturbances were reported in a substantial percentage of the patients. Others have pointed out that derangements of porphyria metabolism do not result in symptoms reported by MCS patients, and that laboratory evaluations of confirmed porphyria-related conditions generally do not resemble those seen in MCS patients (Hahn and Bonkovsky, 1997; Washington State, 1995, 1996b; Gots, 1996).

Other Conditions

Other conditions putatively linked to MCS include systemic lupus erythematosus, chronic fatigue syndrome, fibromyalgia, scleroderma, and multiple sclerosis (NRC, 1992c).

Buchwald and Garrity (1994) compared 30 adults with CFS, 30 with fibromyalgia, and 30 with MCS to evaluate the similarities between these three conditions. The majority of the persons in each group were female. The mean age (40.8–44.0 years) and mean educational level (14.7–14.9 years) of the

three groups were similar. Approximately 80 percent of both the fibromyalgia and MCS groups met the major criteria of the Centers for Disease Control and Prevention's (CDC) CFS criteria (Holmes et al., 1988), and both groups also frequently reported the minor CFS symptom criteria. Persons with MCS most frequently reported adverse effects after exposure to pollution; perfume; and gas, paint, and solvent fumes. However, 53–67 percent of the CFS group and 47–67 percent of the fibromyalgia group also reported adverse effects with exposure to these substances. Persons in all three groups were infrequently employed full time (13–23%) and often were receiving disability (30–57%). The mean number of visits per person to medical providers during the preceding year was 22.1 for persons with CFS, 39.7 with fibromyalgia, and 23.3 with MCS. The investigators concluded that the data, though limited, suggest that these illnesses may be similar, if not identical, conditions. They noted that the diagnosis assigned to an individual with one of these conditions may depend more on the chief complaint and the medical specialty of physicians making the diagnosis than on the actual illness process.

Fiedler et al. (1996) compared 23 persons who had MCS, 13 who had chemical sensitivity (CS), 18 who had CFS, and 18 healthy controls. Individuals with MCS met the full criteria for MCS proposed by Cullen, including an initial identifiable environmental exposure. The individuals with CS met the same criteria for MCS with the exception of a clear onset. Psychiatric and neuropsychological evaluation demonstrated more similarities than differences between the CFS group and MCS and CS groups. In comparison with the control group, the CFS group reported twice as many substances, on average, caused symptoms. However, 30 percent of the CFS group reported that no substance causing illness, and 39 percent reported more than 20 substances. The investigators suggested that investigators may want to consider stratifying individuals with CFS by chemical sensitivities in future studies that evaluate differences between CFS and chemical sensitivities.

In 1994, a conceptual framework and guidelines were proposed for a comprehensive, systematic, and integrated approach to the evaluation, classification, and study of persons with CFS and other fatiguing illnesses (Fukuda et al., 1994). The guidelines specifically stated that MCS and other conditions, including fibromyalgia, that are defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests, do not exclude an individual from the diagnosis of CFS.

Clinical Ecology Approach

Members of the American Academy of Environmental Medicine (AAEM) support the application

of a comprehensive model of environmental medicine (see Section I). A number of definitions and descriptive terms have been developed from this model that are not well known or understood by other clinicians or scientists. The terms were developed in part because physicians practicing clinical ecology believe that these terms and descriptors better define their patients' conditions than do other terms. A basic understanding of these terms gives perspective to the clinical ecology approach to MCS and attendant theories of causation and mechanisms.

The following definitions are taken verbatim from *An Overview of the Philosophy of the American Academy of Environmental Medicine* (AAEM, 1992):

> *Total load* is the sum total at any one time of all an individual's exposures to specific environmental stressors to which he is individually susceptible.
>
> *Adaptation* is the process by which the body attempts to maintain homeostasis in the face of exposures to stressors.
>
> *Maladaptation* is when one or more of the body's biologic mechanisms or systems has been overwhelmed or weakened for various reasons (either acquired and/or genetic), and is not able to maintain homeostasis in the face of the current total load of stressors. Symptoms of illness then occur.
>
> *Deadaptation* allows the body's biologic mechanisms that deal with a particular substance to metabolize, compartmentalize, or excrete it and when this is accomplished, to then reset to a lower set point of nonadaptation, where an acute challenge may then result in an acute measurable reaction.
>
> *Bipolarity of response* refers to the changing manifestations of an ongoing case of Environmentally Triggered Illness being the result of a dynamic continuum of alternating stimulatory and withdrawal states, rather than being a static block of symptoms over time. The phenomenon of bipolarity occurs in all three Stages of Adaptation and consists of a biphasic response: a stimulatory phase upon exposure to a stressor(s) and a withdrawal phase upon withdrawal of a stressor(s).
>
> *Spreading phenomenon* - there are two types. One type refers to the acute or chronic spreading of susceptibility to previously tolerated substances. The second type refers to the acute or chronic spreading of susceptibility to new target organs. Both types of the spreading phenomenon generally occur while maladapting to a

total body overload.

Switch phenomenon manifests clinically as the patient's symptoms switching back and forth over time from one target organ to another, either acutely or more slowly over time. The clinical presentation is further modified by the stage of adaptation that the patient is in at the time.

Individual susceptibility (biochemical individuality) If a group of patients are all susceptible to a particular stressor, each will have a unique individual response to that particular stressor. On the other hand, if a group of patients all share the same clinical symptom due to susceptibilities, each will have his own unique list of stressors that set off that symptom in his case.

Other descriptors used by clinical ecologists include *incitant*, which is a triggering or causative agent (one that induces an allergic or hypersensitive reaction), and *environmental stressor*, which is any substance or situation that has the potential capacity to destabilize homeostasis in a susceptible person (AAEM, 1992).

Summary of Mechanisms

A review of the postulated mechanisms of MCS shows several theories of causation and a considerable body of literature, though not all literature meets current standards of independent peer review. However, definitive data that would confirm or refute hypothesized mechanisms for MCS are generally lacking and those available are confined to a few models of the condition. Because investigators have used different definitions of MCS and because MCS classification in studies is based on self-report, it is difficult to compare patient groups used in various studies to each other or to evaluate the application of theories to the patient groups. Many of the studies are based on an investigator's concept of an etiology for MCS, which may not be compatible with concepts held by others.

Papers written by clinicians and investigators on mechanisms of chemical sensitivity need to be based on sound science and to be capable of passing review for publication in mainstream biomedical journals. Only in this way will they receive review and comment by the entire medical and scientific communities and achieve wider critical review and discussion. Similarly, traditional medical journals need to be open to review and publication of rigorous scientific papers concerning the mechanisms of chemical sensitivity.

IV. Potential Tools for Future Research Studies

Several tools have been suggested as potentially helpful for a better understanding of MCS. This section will focus on biomarkers and environmental control units as two potential tools that may help clarify the nature of MCS.

Use of Biomarkers in Studying MCS

The use of biomarkers in environmental health was described in a series of publications issued by the Board of Environmental Studies in Toxicology of the National Research Council (NRC, 1989a; NRC, 1989b; NRC, 1992a; NRC, 1992b). Biomarkers were defined as "[i]ndicators of events in biological systems or samples" (NRC, 1987) and were further described as "[t]ools that can be used to clarify the relationship, if any, between exposure to a xenobiotic substance and disease" (NRC, 1989b). (The term xenobiotic denotes a chemical substance that is foreign and perhaps harmful to living organisms.) The NRC (1987) classified biomarkers into three categories based on their relation to the exposure-disease continuum. *Biomarkers of exposure* were defined as the identification of an exogenous substance within the biologic system, the interactive product between a xenobiotic compound and the endogenous components, or other events in the biologic system related to exposure. *Biomarkers of effect* were defined as any changes that are qualitatively or quantitatively predictive of health impairment or potential impairment resulting from exposure. *Biomarkers of susceptibility* were defined as indicators that the health of an organism is especially sensitive to the challenge of exposure to a xenobiotic compound.

In practice, most biomarkers are determined by laboratory tests or functional procedures such as spirometry, tactile threshold, or functional brain imaging. Therefore, many of the same considerations that apply to diagnostic tests and procedures in clinical settings also apply to measuring biomarkers in research applications. Clinical applications are discussed in a separate section, while this section focuses on research.

The use of biomarkers has the potential to help elucidate mechanisms of biologic responses to environmental exposures and, therefore, to identify (or substantially exclude) mechanisms responsible for MCS. Biomarkers of susceptibility may be especially valuable probes for identifying persons at risk for MCS. However, to date, the biomarkers yielding the most useful public health

information have been biomarkers of exposure. These include advanced physico-chemical methods that can measure low-level xenobiotics in serum and urine from exposure to: toxic metals (Brody et al., 1994); volatile organic compounds (Ashley et al., 1994); environmental tobacco smoke (Pirkle et al., 1996); pesticides (Hill et al., 1995); aromatic compounds such as dioxins and polychlorinated biphenyls (Pirkle et al., 1995); and other chemical pollutants.

The potential usefulness of biomarker measurements is undermined by either technical or epidemiologic defects (Vineis et al., 1993). Technically, the value of a biomarker can be no greater than the validity of the measurement instrument. Imprecision (poor reproducibility of the measurement) and inaccuracy (significant bias between the measurement result and the true value of the biomarker) can lead to erroneous conclusions in either of two directions: genuine differences can go undetected, or artifactual differences can be created where none really exist (Vineis et al., 1993). The failure to assess and document imprecision and inaccuracy is a frequent shortcoming of research reports addressing biomarkers and MCS, making such findings of little use in public health practice.

The proper use of biomarker tests has been addressed by CDC and ATSDR in a series of reports from workshops and research activities directed at public health investigations at Superfund sites (Hutchinson et al., 1992; Straight et al., 1994; Metcalf et al., 1994; Vogt et al., 1993). These reports recommend that laboratory tests be performed only by laboratories certified under the Clinical Laboratory Improvement Act (CLIA) (Bachner and Hamlin, 1993a; Bachner and Hamlin, 1993b) or engaged in clinical research activities with multicenter quality-assurance programs (Schenker et al., 1993). Tests performed outside these guidelines are often unreliable. The same points apply to biomarkers measured by procedures such as brain scans and neurobehavioral tests, which are often even more difficult to standardize and interpret than laboratory tests (Straight et al., 1995).

Epidemiologic considerations in using biomarkers in public health research are as important as the validity of the measurements. Case definitions of diseases must be specified with sufficient detail and clarity to enable other investigators to reproduce the study. The design must be sound, the investigators and participants properly blinded, the controls suitably selected, and the power of the study must be sufficient to detect differences between the range of normal biologic variation and the expected impact of exposure-related effects. Biomarkers of effect and susceptibility are subject to many confounding physiologic variables such as diurnal variation, stress, nutritional status,

concurrent illness, and other contributors to biologic variability, which should be considered in the study design. Although these considerations are true for any public health investigation employing biomarkers, they deserve special emphasis with respect to studies involving MCS because of the lack of established criteria for a case definition. Of the biomarkers reported to have some association with MCS, virtually none has been tested in blinded studies with well-defined populations using methods documented for precision and accuracy.

The costs associated with proper study design for quality assurance are substantial, but researchers and funding centers must accept these expenses as part of the price of sound public health science. The necessity to support quality assurance has been acknowledged in other public health activities, such as the National Health and Nutrition Examination Survey and the Multicenter AIDS Cohort Study (Schenker et al., 1993), but it has been less well recognized in many environmental health settings, particularly those involving MCS. Fortunately, pilot protocols have been organized to standardize laboratory tests for multi-center environmental health studies (Vogt et al., 1990), and the first multicenter study employing them to examine immune biomarkers in MCS cohorts has been initiated. The value of biomarkers in elucidating mechanisms of MCS should become more apparent as the results from such well-designed studies are reported.

Environmental Control Units

The use of an environmental control unit (ECU) has been suggested by many investigators as a potential means of clarifying MCS mechanisms. An ECU is constructed of nonsynthetic materials that do not release vapors (known as "off gassing") and is ventilated through a filtered, positive-pressure air supply. Furniture within the chamber is constructed of natural, nonsynthetic materials. Attendants and others working in the ECU must not wear dry-cleaned clothing and scented cosmetics. The typical challenge protocol involves placing the patient in the ECU to eliminate exogenous sources of contamination. After a period of time (4-7 days or longer), during which time deadaptation or "unmasking" occurs, the patient is challenged with various potential triggers of symptoms, and reactions are noted (Ashford and Miller, 1991).

An ECU, depending on its use, can be a form of exposure chamber, which is an enclosed space specifically designed for the conduct of inhalation toxicology studies. Exposure chambers are used in animal toxicology studies and some human investigations. They are designed to control precisely the ventilation, temperature, and humidity of the chamber's interior air, and they contain equipment

to carefully deliver measured concentrations of chemicals (e.g., solvent vapors into the chamber. Many protocols have been reported for chambers and have been used for diagnosis, treatment, and research (Selner, 1996).

Many complexities are associated with use of ECUs. Care must be provided around the clock (often a week or longer), along with special clothes, foods, reading materials, and other supplies. The costs of operation and maintenance, therefore, are substantial. Many factors can affect how subjects respond in ECUs. They include temperature range, intensity and type of light in the chamber, and airflow rate. To accurately test chemicals at or near the odor threshold, the use of masking agents has been recommended, although some researchers feel that experiments should begin with a natural, unmasked exposure. Finding an agent that does not cause a response can be difficult (Selner and Staudenmayer, 1995).

Two other points merit comment relevant to the use of ECUs in human subjects research on chemical sensitivity. First is the ethical question of exposing persons to substances in ECUs that may cause them to suffer symptoms of ill health. This kind of ethical concern is considered by Institutional Review Boards, which must review and approve any human research study protocol. Another consideration is the degree to which an ECU represents an unnatural environment to persons who are research subjects. If a person responds positively to being in an ECU, would the experience possibly increase later self-isolation if the patient attempts to re-establish the conditions found in an ECU?

Although these complexities are difficult to overcome, investigators in the United States who have a great deal of experience are using ECUs in their research. Few units are currently in use in the United States, however, primarily because they are very expensive to operate and there are questions concerning their efficacy in routine diagnosis and treatment.

For research purposes, ECUs may offer the possibility of learning whether many of the etiologies and mechanisms suggested for MCS can be validated. Some scientists and physicians believe that valuable information could be gained by the proper use of an ECU (AOEC, 1992; Ashford and Miller, 1991; Miller, 1994; NRC, 1992; Selner, 1996).

Survey Instruments

Questionnaires are one of the most useful tools in epidemiologic investigations. With careful definition of terms, questionnaires can be both an efficient and effective means to collect information about MCS, even in the absence of a consensus case definition. An effective questionnaire will endeavor to define its terms operationally. Questionnaires that have been used in MCS research can be grouped into three subject categories: symptoms, chemicals, and life-style changes.

MCS symptoms questionnaires query the participant about symptoms related to specific organs (e.g., itchy, burning, red, or watery eyes; difficulty focusing) and to constitutional symptoms (e.g., fever and fatigue). Good symptom questionnaires seek to define the symptom, the number of organ systems involved, and the degree of symptom severity.

Questions about the chemicals ask about the substance implicated in the first episode of sensitivity. Information about the number of chemical classes that trigger reactions and the time sequence of the exposure and symptoms is sought. Questions about whether "spreading" of triggering to new chemicals has occurred are also asked.

Assessment of changes in life-style are considered an important way to assess the severity of MCS. Questions about changes in diet, working, and shopping are asked. Changes in home furnishing and clothing may also be queried.

V. Public Health Issues in Medical Evaluation and Care of MCS Patients

Many physicians are uncertain how to approach the evaluation and care of persons who have multiple symptoms that attribute to low-level chemical exposure. Although medical approaches and therapies differ considerably because of differing beliefs about MCS by physicians, all individuals who report suffering from chemical sensitivities should receive a competent, complete medical evaluation and compassionate, understanding care. The goal of this care should be to promote health without causing additional harm. Individuals should not be subjected to ineffective, costly, or potentially dangerous treatments. Appropriate care for well-characterized medical and psychological illnesses should not be withheld or delayed. The ramifications of recommending functional changes in workplace or home settings should be carefully considered.

Medical Evaluation

The identification of MCS is based largely on the patient's description of the symptoms and the relationship of these symptoms to environmental exposures. The evaluation of an individual for MCS should, therefore, begin a complete and detailed history, including a comprehensive exposure history. The *ATSDR/NIOSH Case Study in Environmental Medicine—Taking An Exposure History* (ATSDR, 1992) is a useful guide for physicians unfamiliar with taking an environmental exposure history.

MCS patients often report that their symptoms began after an accidental overexposure to a chemical, typically a solvent or a pesticide, and that their symptoms recurred following exposure to lower levels of the same chemical. Symptoms then began to occur in response to low-level exposure to an increasing number of other chemicals, often unrelated to the initiating compound. Commonly reported symptoms are listed alphabetically in Table 4 and, therefore, are not in any order of frequency of occurrence.

MCS patients often associate symptoms with such substances as colognes and perfumes, aerosol air freshener, laundry detergent, gasoline exhaust, cleaners, insecticide sprays, and cigarette smoke (Ziem, 1992; Lax and Henneberger, 1995). Miller (1995) reported that an acquired, self-identified intolerance to alcohol is notably frequent among MCS patients.

Table 4: Commonly Reported MCS Symptoms.

Commonly Reported MCS Symptoms	
Breathing difficulty	Headache
Chest pain	Inability to concentrate
Depression	Joint and muscle pain
Eye, ear, nose, throat irritation	Malaise
Fatigue	Memory loss, confusion, dizziness
Gastrointestinal problems	Skin disorders

Although physical findings and the results of laboratory tests in MCS patients are typically within normal limits (ACP, 1989), the physical examination, laboratory evaluation, and psychological assessment should be sufficiently comprehensive to establish or exclude underlying and coexisting medical conditions that are amenable to treatment. Physicians should be careful not to overlook other medical conditions that are amenable to treatment in an MCS patient.

No test result or panel of results can currently identify MCS. A number of tests have been suggested for evaluating MCS or have been used in studies of patients with MCS or chemical sensitivities; such tests include immunologic assays, quantitative electroencephalography, brain electrical activity mapping, evoked potentials, positron emission tomography, and single photon emission computed tomography. However, no laboratory test has been validated for sensitivity or specificity as a diagnostic predictor of MCS.

Physicians should recognize that classifying a condition as MCS does not explain the pathogenesis of the disorder. NRC's Subcommittee on Immunotoxicology advised that, "[w]henever possible, the term ***multiple chemical sensitivity*** should be replaced with a specific diagnosis to avoid the confusion between diagnosis and etiology that is inherent in the term." Some clinicians do not believe that MCS is a distinct disease and will not diagnose MCS under any circumstances (Cullen, 1994).

1135

1136 **Treatment**

1137 Different treatment approaches for MCS have been described that parallel the proposed mechanisms.
1138 Treatment modalities that include avoidance of chemicals, megavitamins, restricted or rotation diets,
1139 provocation-neutralization, sauna detoxification, and psychiatric treatment have been suggested
1140 (Ziem, 1992; AAEM, 1992; Simon, 1992). The effectiveness of these treatments has not been
1141 demonstrated. Because the etiology of MCS is unknown, the primary goals of most physicians are
1142 aimed at relieving symptoms and improving function. With an absence of data from definitive
1143 clinical trials, no conclusions about the optimal choice of treatment modalities can currently be
1144 made. However, aggressive therapies of unproven benefit that are potentially harmful cannot be
1145 recommended.

1146

1147 Health-care providers must recognize the fundamental obligation to "First, do no harm." Ill persons
1148 must not be subjected to costly, time-consuming, ineffective, or dangerous therapeutic regimens.
1149 Care-givers must ensure that their treatment methods meet the standards of peer review and tests
1150 of efficacy, and offer reports on such treatment methods in the open and critically reviewed
1151 literature.

1152 Persons identified as having MCS also need to be educated about what is known and not known
1153 about MCS. MCS patients should be informed about the lack of proven efficacy for various
1154 treatments and cautioned about costly and potentially harmful treatments. Avoidance of some
1155 exposures may be warranted, but recommendations of complete avoidance of chemical exposures
1156 should not be made without considering the impact of such restrictions. Major lifestyle
1157 modifications can have substantial consequences, including the loss of social support and
1158 employment. Because some individuals who have symptoms of MCS suffer social and psychological
1159 consequences of their condition, health care should be supportive.

VI. Organizational Statements Relating to MCS

Several organizations have issued formal statements about MCS. Selected portions of several of these statements are presented here. The statement of the American Academy of Environmental Medicine (AAEM) differs from those of other medical organizations. All these statements request the caring and compassionate evaluation of the MCS patient.

United States:

AAEM has published its philosophy in *An Overview of the Philosophy of the Academy of Environmental Medicine* (AAEM, 1992). This statement suggests that the nature of system dysfunctions can best be elucidated by the application of a comprehensive model of environmental medicine. Definitions of key terms used in their model were presented in Section III. The *Overview* also presents in detail AAEM's approaches to the diagnosis and treatment of MCS.

A number of other medical organizations have also issued formal statements about MCS or closely related issues. These include the American Academy of Allergy, Asthma and Immunology (1986, 1997), the American College of Physicians (1989), the American College of Occupational and Environmental Medicine (1991), and the American Medical Association (1992). Their statements are, in general, skeptical of MCS as a distinct disease entity and critical of the quality of MCS research. The following examples represent the viewpoints contained within these statements.

The American Academy of Allergy, Asthma and Immunology, which updated their position statement in 1997, included the following in their statement: "[B]ecause of the subjective nature of the illness, an objective case definition is not possible. Allergic, immunotoxic, neurotoxic, cytotoxic, psychological, sociologic, and iatrogenic theories have been postulated for both etiology and production of symptoms. There is no scientific evidence to establish any of these mechanisms as definitive. . . A causal connection between environmental chemicals, foods, and/or drugs and the patient's symptoms is speculative and not based on the results of published scientific studies."

The American College of Physicians (1989) concluded that provocation-neutralization therapy is unproven. They recommended that clinical ecologists who want to definitively study provocation-neutralization testing and neutralizing therapy establish a precise definition of the condition to be

diagnosed and treated, and document the fact that study subjects meet this definition.

The American College of Occupational and Environmental Medicine (1991) stated their views on multiple chemical hypersensitivity syndrome (MCHS), commenting "[I]t is the position of the American College of Occupational and Environmental Medicine (ACOEM) that the MCHS is presently an unproven hypothesis and current treatment methods represent an experimental methodology. The College supports scientific research into the phenomenon to help explain and better describe its pathophysiological features and define appropriate clinical interventions."

The American Medical Association (AMA) (1992) includes in their position statement on clinical ecology: "[U]ntil such accurate, reproducible, and well-controlled studies are available, the American Medical Association Council on Scientific Affairs believes that multiple chemical sensitivity should not be considered a recognized clinical syndrome." A subsequent report, *Indoor Air Pollution*, which was coauthored by the American Lung Association, AMA, the Consumer Product Safety Commission, and EPA stated that "[T]he current consensus is that in cases of claimed or suspected MCS, complaints should not be dismissed as psychogenic, and a thorough workup is essential. Primary care givers should determine that the individual does not have an underlying psychological problem and should consider the value of consultation with allergists and other specialists" (American Lung Association, 1995).

In addition, the published statements from all these groups have called for further study and publication in peer-reviewed journals of other specific research areas, including adaptation/deadaptation, spreading, and diet rotation techniques.

International:

In February 1996, a workshop organized by the International Program on Chemical Safety (IPCS)[2] in collaboration with several of Germany's federal health and environmental agencies met in Berlin to discuss multiple chemical sensitivities. Invited participants represented a range of disciplines involved in researching, investigating, and treating MCS and other environmental illnesses. The

[2] IPCS is jointly sponsored by the World Health Organization, the International Labor Office, and the United Nations Environmental Program.

majority of the invited participants suggested that the term "idiopathic environmental intolerances" (IEIs) should be used to describe MCS, because they concluded that there were neither accepted theories of underlying mechanisms nor validated clinical criteria for diagnosis, and a relationship between exposures and symptoms was unproven (IPCS, 1996).

The recommendations of the workshop included the use of the descriptor IEI only after a thorough examination of patients, careful consideration of alternative explanations, and focused interdisciplinary approaches for the diagnosis and treatment of these patients. Research recommendations included challenge studies to distinguish psychogenic from toxicogenic or other responses and epidemiologic research directed at the prevalence of relevant symptoms and demographic, time, and disease correlates. There was a call (1) for communication and cooperation between all responsible health-care systems, institutions, and insurers to coordinate approaches to patient care; and (2) for the promotion, through the World Health Organization (WHO) of a continuous exchange of knowledge and international cooperation on research into IEI.

After the meeting, controversy arose about the workshop's conclusions and recommendations that were sent to the workshop attendees (Abrams et al., 1996; Dayan, 1996; Goldman et al., 1996; Mercier et al., 1996), and no final report has been issued. However, a summary of the workshop's recommendations can be found elsewhere (Lessof, 1997).

VII. Key Panels, Workshops, and Reports: Recommendations

Since 1990, federal government agencies have sponsored or cosponsored a number of expert panels and workshops concerning MCS. These meetings have been important, because key researchers on chemical sensitivity and related areas have participated in the development of recommendations pertinent to the condition. MCS patient advocates and persons with MCS have also participated in some of the panels and workshops. The workgroup recognizes the expertise used to develop the recommendations from these meetings and is concerned that they not be lost to time. Moreover, it is important to compare the status of the key recommendations to assess whether they are still relevant for a better understanding of MCS. The key recommendations from federally sponsored panels and workshops on MCS are given in Table 5. The key recommendations from individual panels and workshops are described in the following sections.

NRC Workshop on Multiple Chemical Sensitivities, 1991

In March 1991, at the request of EPA, the National Research Council (NRC) conducted a workshop to develop a MCS research agenda. The participants included a wide range of scientific disciplines and philosophical views. The meeting reported its findings and recommendations through three working groups: Research Protocol for Clinical Evaluation, Exposures and Mechanisms, and Epidemiology.

Key Recommendations:

Clinical Evaluation working group:

- Prospective longitudinal studies of exposure-based events are very important and should be performed.
- A research priority should be the study of the adaptation-deadaptation hypothesis, and the study should be pursued using an ECU. In addition, a second approach should evaluate individuals, over time, in their usual environment.
- Selection of research subjects should be based on the specific hypothesis to be tested (e.g., symptom-based, exposure-based, and population-based).
- Development of a database of chemicals, foods, drugs, and signs and symptoms reported to be associated with MCS is important.

Exposures and Mechanisms working group:

- Studies should include a comprehensive history, including exposures, physical examination, and appropriate laboratory testing. Endpoints for response should include immunologic, neurologic, endocrinological, psychological, social, and other markers or measures.
- Dose-response relationships should be examined.
- Animal models should be developed that mimic the human syndrome.
- Tissues obtained by biopsy and necropsy from patients, animals, and their controls should be evaluated for signs of pathologic change.

Epidemiology working group:

- The magnitude of the problem caused by MCS in the general population should be determined.
- Multi-center, clinical case-comparison studies in occupational/environmental medicine clinics should be an early priority.
- A broad set of symptom prevalences should be utilized that will allow flexible construction of a variety of case definitions.
- Population-based methods, including construction of survey instruments, should be used to determine the basic descriptive epidemiology of certain multiorgan disorders that have been linked to MCS (e.g., systemic lupus erythematosus, scleroderma, multiple sclerosis, and somatization disorder).
- Prompt studies of defined populations subjected to discrete and sudden chemical exposures should be enacted to assess the initiation and natural history of sensitivity syndromes involving environmental chemicals.
- Normal ranges for new test modalities, including the sensitivity and specificity of screening techniques and biomarkers, should be determined.

AOEC Workshop on Multiple Chemical Sensitivity, 1991

In September, 1991, the Association of Occupational and Environmental Clinics (AOEC) held an MCS workshop in Washington, D.C. The workshop format included plenary sessions and four work groups that focused on research needs in characterizing patients, events, developing treatment strategies, and exploring possible mechanisms.

Key Recommendations

Characterizing Patients group:

- Develop a case definition for use in descriptive epidemiologic research and in challenge studies.

Characterizing Events group:

- Determine incidence and prevalence of MCS, perhaps by using community-based studies and existing surveys such as the National Health and Nutrition Examination Survey.
- Carry out prevalence surveys in specific occupational cohorts and cross-cultural studies of "naive" populations (i.e., groups who are unaware of MCS).
- Perform longitudinal studies of populations exposed through "natural" situations (e.g., "sick building" exposures).
- Develop case registries to follow the course of MCS patients.
- Carry out double-blind, placebo-controlled challenge studies, primarily inhalation studies, including but not limited to chamber studies.

Treatment Methods group:

- Study the effects of early intervention in an exposed population (e.g., critical incident counseling).
- Perform randomized, controlled trials of therapies that have some reasonable theoretical basis.
- Carry out studies of subjective outcomes, including belief structures of both patients and health-care providers.

Mechanisms group:

- Perform challenge studies, primarily inhalation studies, including (but not limited to) chamber studies.
- Study olfactory function and the nasal-olfactory-limbic pathway.
- Develop studies of neuroimaging techniques (e.g., PET and SPECT) and studies of pharmacologic probes.
- Conduct prospective studies of cohorts of persons sensitive to chemicals and of families of MCS patients.

Report on Biologic Markers in Immunotoxicology, 1992

In addition to the findings and recommendations from the March 1991 NRC Workshop, in 1992, the NRC Subcommittee on Immunotoxicology, through its Committee on Biologic Markers, published *Biologic Markers in Immunotoxicology*. The report endorsed the recommendations from the NRC meeting held in 1991.

ATSDR Expert Panel on Multiple Chemical Sensitivity, 1993

In fiscal year 1993, Congress appropriated $250,000 to ATSDR "[f]or chemical sensitivity/low level chemical and environmental exposure workshops." The appropriation was in response to community concerns that chemical releases from hazardous waste sites and pesticide applications were associated with MCS. In response, ATSDR formed a 12-person panel to provide advice to the agency on projects that would fulfill congressional intent. The panel comprised representatives from academia, medicine, public health, and industry as well as several MCS patient advocates. Government and outside observers were also present. In April 1991, the panel developed and ranked ideas for MCS projects (Clean Sites, 1993).

Key Recommendations

- Convene a neurologic workshop with clinicians and neuroscientists to compare clinical observations with animal and other neurologic research findings.
- Conduct a cross-sectional/prevalence epidemiologic study.
- Use a panel of experts with diverse interests to design and monitor a study that would use an existing ECU. The project would involve testing the usefulness of techniques such as double-blind, placebo-controlled challenge testing, provocation-neutralization, and deadaptation.
- ATSDR should convene an interagency committee and obtain funds for an environmental unit. ATSDR should develop an educational workshop for other agencies to prepare them for membership on the interagency committee.
- Convene a committee to define single or group phenomena to describe chemical sensitivity (i.e., MCS).
- Convene an MCS panel to focus on developing a database, ways to piggy-back field-study research, and a registry.

Chemicals and Neurobiologic Sensitivity, 1994

In April 1994, as a part of ATSDR activities that responded to the Congressional mandate to fund MCS workshops, and in response to the recommendations of the expert panel meeting held in April 1993, a national meeting was held in Baltimore, Maryland, to discuss low-level exposure to chemicals and neurobiologic sensitivity.

The conference did not formally adopt findings or recommendations. However, an overview was prepared and presented (Kipen, 1994); this overview pointed out that some overall recommendations could be made that do not necessarily represent consensus but may be useful to interested parties:

Definitions:

- Establish a case definition with attention to its validity (e.g., content, criteria, and predictive value).

Populations:

- Explore large populations for salient characteristics of chemical sensitivity.
- Determine population prevalence of the various degrees of chemical sensitivity, with or without co-morbid medical or psychiatric conditions.
- Undertake analytic epidemiology studies to ascertain risk factors and eventually design prevention strategies.

Mechanisms:

- Focus on the olfactory system, both as a chemical sense organ and as an important receptor for psychological cues.
- Focus on the immune system, especially its ability to be conditioned by psychological stimuli; include the field of psychoneuroimmunology.

California Department of Health Services, 1994

To further address the recommendations from the ATSDR expert panel meeting held in 1993, a portion of the funds appropriated by Congress to ATSDR were used to fund a grant to the California Department of Health Services (CDHS). The grant's purpose was to develop a scientifically acceptable research design that could identify persons with physiologically-based susceptibility to low levels of chemical exposure. The grant included determining a case definition for MCS, designing survey instruments, and selecting appropriate biomarkers to characterize individuals who report sensitivities to multiple chemicals. In 1994, an expert panel was assembled by CDHS to

provide advice on how best to carry out these goals. In 1996, CDHS released a final report on the project (CDHS, 1996).

Key Recommendations:

- Rather than using a compromise definition, CDHS proposes the use of questionnaire data to assemble diagnostic scales describing various characteristics and attributes of the MCS syndrome.
- Population-based determinations of prevalence of MCS are an important step in evaluating hypotheses about the mechanisms and etiology of this condition. Questions about the MCS syndrome have been included in the 1995 California Behavioral Risk Factor Survey (BRFS). CDHS has also proposed a more extensive study using the questionnaire they have developed.

NIEHS, MCS: Controlled Exposure Studies, 1995

As part of NIEHS activities related to the Superfund Hazardous Substances Basic Research and Training Program, a workshop was held by the Environmental and Occupational Health Sciences Institute, the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, and Rutgers University. The objective of the workshop was to develop a multidisciplinary research agenda for elucidating possible mechanisms for MCS that involved investigators who realized the interactive nature of the problem. The relevant disciplines included neuroscience, immunology, epidemiology, exposure assessment, and environmental chemical engineering.

Key Recommendations:

- Clear criteria are needed for the selection of subjects to participate in studies of chemical sensitivities, for example, the inclusion/exclusion of MCS subjects with co-morbid diagnoses. If subjects with other medical illnesses (e.g., asthma) are included, the number of co-morbid diagnoses should be limited in any given study and controlled in the analyses.
- Controlled exposure studies in which a carefully defined set of MCS subjects are exposed to a chemical hypothesized to cause symptoms and in which objective and subjective responses are measured is critical. At present, no controlled study has demonstrated a relationship between chemical exposure and symptoms in this patient

group.

- Effects of conditioning and sensitization need to be considered in research studies of controlled exposure.
- Consideration should be given to single case designs as an alternative to group comparisons, given the heterogeneity of subjects, symptoms, and chemical exposures.

EOHSI/NIEHS Conference, 1996

In September 1996, the Environmental and Occupational Health Sciences Institute (EOHSI) and NIEHS sponsored the Conference on Experimental Approaches to Chemical Sensitivity, which was held in Princeton, New Jersey (Kipen and Fiedler, 1997). It was conducted as a workshop in which experienced MCS clinicians who could document patient characteristics worked with experimental investigators from MCS-relevant disciplines to develop experimental approaches to MCS elucidation. Five working groups addressed specific topics: empirical approaches for the investigation of toxicant-induced loss of tolerance, Pavlovian conditioning and MCS, psychoneuroimmunology, neurogenic inflammation, and testing the neural sensitization and kindling hypothesis. Each group was composed of both persons who had experience in trying to treat MCS patients and researchers who had developed research methods relevant to the MCS model under discussion. Each group produced recommendations, which included the following (Bascom et al., 1997; Bell et al., 1997; Cohen et al., 1997; Miller et al., 1997; Siegel et al., 1997):

Key Recommendations:

- Studies should be initiated to test hypotheses in the domain of nonneurogenic inflammation, determining whether inflammation is present in symptomatic tissues of patients who have MCS and if it is associated with a heightened neurosensory response.
- Conduct longitudinal studies to test hypotheses: (1) a psychoneuroimmunologic component is correlationally or causally associated with development of MCS and (2) stress is associated with MCS as a chronic disabling disease.
- Conduct double-blind, placebo-controlled challenge studies performed in an environmentally controlled hospital facility coupled with rigorous documentation of both objective and subjective responses.

- Conduct interviews with MCS patients to ascertain episodes consistent with a learning interpretation of their symptoms.
- Conduct balanced placebo-controlled studies to separate the effects of chemical expectation from chemical effects in MCS.
- Evaluate the possibility of olfactory hypersensitivity in MCS patients through further research.
- Systematically evaluate the efficacy of systematic desitization as a treatment for MCS disorders.
- Consider single-case designs as an alternative to group comparisons, given the heterogeneity of subjects, symptoms, and chemical exposures.
- Develop a generally accepted structured interview that is based on common patterns of patient symptoms.
- One design for protocols to initiate and test for sensitization in MCS patients could involve the same sensitization procedures but compare outcomes under conditions of masking and unmasking.
- Test the hypothesis that MCS patients are more susceptible to initiation of context-dependent sensitization than are control subjects.
- Longitudinal studies with repeated measures would enable evaluation of fluctuations over time.
- Conduct laboratory animal studies to assess neural time-dependent sensitization mechanisms.

DHHS Report to Congress, 1998

In January 1998, the Acting Assistant Secretary for Health, Department of Health and Human Services (DHHS), submitted a report to Congress entitled "Report to Congress on Research on Multiple Chemical Exposures and Veterans with Gulf War Illnesses" (Eisenberg, 1998). The report was prepared in response to House Report 105-205, which accompanied the Departments of Labor, Health and Human Services, and Education and Related Agencies Appropriations Bill for fiscal year 1998. The appropriations language states, "[T]he Committee believes that there is need to conduct research as rapidly as possible into the possible links between chemical and biological exposures and the illnesses suffered by tens of thousands of Persian Gulf War veterans. The Committee believes it would be useful to support research in areas of multiple chemical sensitivity; the

definition of individual genetic differences in the ability to metabolize environmental agents commonly encountered during the Persian Gulf War; and the development of a better understanding of how multiple exposures of chemicals interact to exert their toxicity on an organism. . . The Committee requests the Secretary to submit a report by December 31, 1997 describing the Department's proposed Gulf War illness research plan and a description of how funding will be allocated among the DHHS agencies to implement the program."

The DHHS report indicates that a representative will be located in the Office of Public Health, Office of Secretary, as the principal official for the research program stipulated by Congress. In fiscal year 1998, a consensus-building conference will be held to "[f]ully characterize the nature of multiple chemical exposures with the Gulf War veteran population and to relate this characterization to what is known about Multiple Chemical Sensitivity (MCS) and related conditions and disorders within civilian populations." CDC will be allocated $300,000 to conduct the conference. Also, in fiscal year 1998, $400,000 will be added to an NIH grant entitled "Chemical Mixtures in Environmental Health."

Summary

Table 5 lists, in descending order of concordance, the recommendations from the seven meetings that are described in this section. There were four recommendations that had support from five or more meetings:

- Conduct basic epidemiology,
- Conduct case-comparison studies,
- Develop a case definition for MCS, and
- Conduct challenge studies.

The specifics of these four recommendations varied across the seven meetings. For example, all meetings recommended more research, although the specific types of research varied with the meeting. The need for more basic epidemiologic data on MCS was a mutual theme at all seven meetings.

This discussion of the previously held federally-supported meetings, while presenting the formal recommendations, should not diminish the serious consideration that was given to many other topics. The published proceedings should be reviewed for additional details. As will be evident in the next

1496 section, only limited progress has been made by federal agencies on many of the recommendations
1497 listed in Table 5.

Table 5: Recommendations from Selected Meetings about MCS.

Recommendation	NRC 1991	AOEC 1991	ATSDR[1] 1993	ATSDR[2] 1994	CDHS 1994	NIEHS 1995	EOHSI NIEHS[3] 1996
Basic epidemiology	X	X	X	X	X		X
Case-comparison studies	X	X		X	X	X	X
Definition development	X	X	X	X	X	X	
Challenge studies	X	X	X			X	X
Studies of exposed pop. incidents	X	X			X		X
Studies in ECU	X	X	X				X
Neuro. research		X	X	X			
Olfactory research		X		X			X
Study of clinical ecology hypotheses	X	X					X
Case registries		X	X				
Determine epi. of related conditions	X			X			
Animal studies	X						X
Federal interactions			X				
Immune research				X			
Studies of therapies		X					
Inventory causative factors	X						

[1] Expert Panel Meeting; [2] Chemicals and Neurobiologic Sensitivity Meeting; [3] Environmental and Occupational Health Sciences Institute/National Institutes of Environmental Health Sciences Meeting.

VIII. Federal Actions

The following statements have been prepared by each of the agencies represented in the workgroup. They describe their past and current activities related to low-level chemical sensitivity research and any future initiatives. It is hoped that these overviews will help in coordinating plans and further actions. The presentations also show the range of federal activities with regard to MCS.

Agency for Toxic Substances and Disease Registry

ATSDR, under its authorities in the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA), has maintained interest for several years in issues surrounding sensitivity to low levels of chemicals because these kinds of exposures can occur in populations who live near hazardous waste sites, which are the focus of CERCLA. Given the need for additional scientific research, ATSDR provided financial support for two conferences focused on MCS: the first meeting was sponsored by the National Academy of Sciences (NAS) in March 1991, and the second was sponsored by the Association of Occupational and Environmental Clinics (AOEC) in September 1991.

In fiscal year 1993, Congress appropriated $250,000 to ATSDR for "[c]hemical sensitivity and low-level chemical and environmental exposure workshops." The first effort under this mandate was to convene an expert panel in April 1993. Out of the deliberations of this panel came a number of recommendations that resulted in the following actions: (1) a conference on Low Level Exposure to Chemicals and Neurobiologic Sensitivity, Baltimore, Maryland, April 1994; (2) publication of the proceedings from that conference, as well as an additional publication containing the proceedings from three federally sponsored conferences on MCS (i.e., the NRC 1991, AOEC 1991, and ATSDR 1994 conferences); and (3) an award to the California Department of Health Services "[t]o develop a controlled, scientifically acceptable research design which will test the hypothesis that there is a group of individuals with physiologically based susceptibility to low levels of chemical exposure."

Throughout these efforts, ATSDR has served as a conduit of information about the issues surrounding MCS and has encouraged clinical and other research to add to the knowledge base concerning low-level chemical sensitivity. ATSDR has no on-going or planned research activities

specific to MCS.

Department of Defense

The Department of Defense (DoD) is sponsoring several projects with significance for better understanding multiple chemical sensitivity. Studies include investigation of the dysregulation of the normal neuroendocrine-mediated stress response which may lead to a better understanding of common underlying pathophysiologic mechanisms in fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivity and the undiagnosed illnesses of Gulf War veterans. Another study is examining neuropsychological function in a group of treatment-seeking Gulf War veterans and non-deployed Gulf era veterans. One of the objectives of this study is to ascertain the prevalence of multiple chemical sensitivity-like symptoms reported among the male and female study population, and to explore risk factors for development of this condition.

DoD employees operate in unique work environments. The Department will continue to provide appropriate occupational health and industrial hygiene programs to minimize potential workplace exposures to hazardous chemicals. DoD will also continue to design and conduct essential health education, and provide safety equipment and engineering controls to minimize or eliminate exposures to known chemical and other workplace hazards. The Department's highest priority is to continue to provide a safe work environment for all DoD employees.

Department of Energy

As the employer of more than 100,000 federal and contractor employees, the Department of Energy (DOE) is interested in developments in MCS. An informal sampling of the Department's occupational health clinics revealed occasions of workers complaining of possible MCS symptoms. Some of the clinic medical directors suggested that MCS may become a larger concern for DOE and would value guidance from the workgroup. There are currently no uniform diagnostic criteria or treatment protocols in use at DOE sites.

Department of Veterans Affairs

The Department of Veterans Affairs (DVA) has funded three Environmental Hazards Centers for the purpose of conducting research on environmental health and toxicology related to military service. At this time, these centers are all involved in research on Persian Gulf veterans' illnesses.

Two of the centers include research involving MCS in their research protocols.

At the Boston Environmental Hazards Center, the physical and psychological health of a cohort of Gulf War veterans has been followed longitudinally since their return from the Persian Gulf. A subset of these veterans is being examined intensively with protocols addressing MCS and other conditions; diagnoses of MCS, based on the Cullen criteria, are being made as appropriate. Detailed studies of those diagnosed with MCS include psychiatric status, neuropsychological function, symptom reports, occupational and economic outcomes, pulmonary function, neurologic status (central nervous system [CNS], peripheral nervous system [PNS], autonomic nervous system [ANS] with sophisticated neuroimaging and neuropsychological assessment), and evaluation of stressors (i.e., social, war trauma, and/or exposure to environmental hazards).

At the East Orange Environmental Hazards Center, an epidemiologic study of Persian Gulf Registry and nonregistry veterans is being conducted that will allow diagnosis of MCS, CFS, and other disorders. A cross-sectional study is being done of several categories of veterans: those with MCS but without CFS, those with CFS without MCS, and those having both CFS and MCS. Control subjects are being tested for viral/immunologic measures; psychiatric, psychological, and neuropsychological function, and autonomic deregulation. An experimental study is also planned at East Orange in which 40 MCS subjects will be exposed to two stressors (i.e., exercise and exposure to phenyl ethyl alcohol) and will undergo several preexposure and postexposure measures, including assessment of symptoms, neurobehavioral performance, nasal lavage cellularity, RNA levels of cytokine gene expression, and autonomic reactivity.

National Center for Environmental Health, CDC

CDC's National Center for Environmental Health (NCEH) was established to promote health and quality of life by preventing and controlling disease, injury, and disability associated with the interactions between people and their environment outside the workplace. The impact of its programs is amplified through close interaction with public health departments in every state and with many public, private, and international organizations. Its major activities include biomonitoring for environmental toxicants, lead poisoning surveillance and prevention, birth defects surveillance and prevention, and exigent public health investigations where environmental exposures may be involved.

NCEH does not have any programs directly devoted to MCS; however, a number of its activities are relevant to the issues surrounding MCS. Through its division of Environmental Health Laboratory Sciences (EHLS), NCEH has a unique leadership role in measuring more than 200 toxicants in human biologic samples. Analyses of samples from large population studies have established the extent of exposure in the U.S. population to volatile organic compounds, pesticides, halogenated aromatic compounds (e.g., PCBs), toxic metals (e.g., lead and cadmium), and environmental tobacco smoke. This information helps to clarify relationships between exposures to toxicants and human health effects.

NCEH has also addressed the use of laboratory tests as biomarkers of susceptibility and health effects, concentrating on target organs such as the liver, kidney, and immune system. NCEH provides national reference laboratory capability for tests of immune status and function, including lymphocyte phenotyping, serum mediator measurements, and various assays of actual immune function. Standardization of these tests for immune status has been a particular focus at NCEH, whose investigators have collaborated with NAS, ATSDR, and AOEC to establish guidelines for the proper use of these tests and apply them to public health studies.

A number of epidemiologic investigations conducted by NCEH have relevance to questions of chemical sensitivities. Epidemiologists in the Division of Environmental Health Hazards and Health Effects have investigated adverse health effects associated with tryptophan ingestion, inhalation of fuels and other air pollutants, and fetal alcohol exposure. A community-based program in asthma prevention will explore risk factors and intervention effectiveness for this increasingly important cause of morbidity and mortality. At present, there is no specific funding or legislative mandate within NCEH in the area of MCS.

National Institute of Environmental Health Sciences, NIH

The mission of NIH's NIEHS is to reduce the burden of human illness and dysfunction from environmental exposures by understanding the interrelationship between exposure, individual susceptibility, and time. NIEHS has provided research support to studies related to MCS and to areas of research associated with MCS outcomes.

Research activities funded by NIEHS related to chemical sensitivity focus primarily on (1) exposure

and organ and system toxicology and (2) genetic susceptibility of exposure. It appears that environmental agents can trigger a variety of disorders in susceptible persons. Some susceptible persons apparently respond to extremely low levels of chemicals in the environment by expressing multiple symptoms in one or more organ systems, frequently involving the central nervous system. Such chemical exposures and symptoms appear to be associated with proximity to hazardous waste sites, other community exposures, indoor air pollution, and industrial activities. Pesticides and solvents are the two major classes of chemicals most frequently reported by patients reporting low level sensitivities as having initiated their problems.

NIEHS has also supported a number of workshops and meetings concerning MCS. In September 1995, the NIEHS Superfund Hazardous Substances Basic Research and Training Program supported a workshop in Princeton, New Jersey, entitled *Multiple Chemical Sensitivities: Controlled Exposure Studies*. This workshop brought together a number of leading investigators in the field to assist NIEHS in developing new and innovative research ideas to better understand MCS. The overall objective of the meeting was to develop experimental approaches for testing the relationship between chemical exposures and the symptomatology expressed by patients with chemical sensitivities.

National Institute for Occupational Safety and Health, CDC

CDC's National Institute for Occupational Safety and Health (NIOSH) receives hundreds of requests annually for information on MCS. An estimated 200-400 requests are received through NIOSH's toll-free telephone number. NIOSH sends information about MCS to these requestors.

NIOSH conducts workplace health hazard evaluations at the request of workers, employers, and government agencies. A small number of requests have included mention of MCS in combination with a variety of other concerns.

U.S. Environmental Protection Agency

EPA has occasionally received reports from individuals of symptoms that they attributed to chemical sensitivity subsequent to pesticide or other chemical exposures. Some EPA employees have also reported complaints of chemical sensitivity that they attributed to workplace or other exposures to various substances. EPA is interested in understanding the scientific basis for the development of

effects following exposures at much lower levels than average, the exposures that produce such effects, and the quantitative relationships between them.

Research activities related to chemical sensitivity are being conducted by EPA as part of the agency's health research program on indoor air pollutants. EPA's statutory authority for indoor-air issues and problems enables the agency to engage in research and information dissemination rather than regulation, enforcement, or other control activities. In the indoor air health research program, research is being performed to (1) understand the relationship between exposure to and effects of selected biocontaminants; (2) develop methods and understand the risks posed by low levels and mixtures of indoor organic vapors; and (3) understand the dimensions and characteristics of susceptible populations, including those who report multiple chemical sensitivity. The goals of the research on susceptible populations are to identify such populations and evaluate the determinants of susceptibility, with current emphasis on clinically characterizing those persons who report having chemical sensitivity.

Part of the difficulty with conducting MCS research is identifying objective, quantifiable indicators for classifying research subjects in order to study their conditions in greater depth. An NAS workshop was initiated and funded by EPA's Indoor Air Division to identify research needs for MCS. Scientists from EPA's National Health and Environmental Effects Research Laboratory (NHEERL) also participated in the workshop, from which emerged a recommendation that careful clinical characterizations be done on persons reporting MCS to identify cases for additional study. In response to this recommendation, NHEERL scientists developed a protocol and initiated a pilot study to evaluate persons reporting MCS symptomatology on the basis of exposure history and symptoms; medical history and examination; psychiatric evaluation; and a profile of clinical medical, psychological, and physiologic parameters and test results. The purpose of this pilot study was to generate hypotheses that are feasible to test. Data were collected over an extended period of time on a small group of subjects who self-reported chemical sensitivity. NHEERL has not yet reported its findings.

In addition, EPA scientists are communicating and coordinating with other organizations involved in research on MCS. Besides cosponsoring and participating in the NAS workshop, EPA has coordinated with ATSDR to ensure mutual understanding of both agencies' efforts on MCS. NHEERL scientists have made invited presentations about MCS to the Toxicology Forum (Summer

1993) and the American College of Allergy and Immunology (Fall 1993). EPA participated in the ATSDR-sponsored MCS meetings held in 1993 and 1994. NHEERL is actively pursuing collaborative exchanges of information with investigators from the academic community (e.g., the University of Medicine and Dentistry of New Jersey and Yale University). NHEERL scientists have also published articles addressing MCS-related research issues (Dyer and Sexton, 1996; Dyer, 1997).

Summary of Federal Actions

This section summarizes past and current MCS-related activities conducted by the departments and agencies that constituted the workgroup. As noted in Section VII, there were four recommendations that had support from four or more of the meetings described in that section. It is possible to relate the MCS-related activities with the workshop recommendations, as denoted below.

- *Conduct basic epidemiology*—ATSDR funded the California MCS prevalence study; no other epidemiologic studies are currently being sponsored by the workgroup's agencies.

- *Conduct case-comparison studies*—EPA scientists have developed a protocol and initiated a pilot study to evaluate persons reporting MCS symptomatology on the basis of exposure history and symptoms; medical history and examination; psychiatric evaluation; and a profile of clinical medical, psychological, and physiologic parameters and test results. The Department of Veterans Affairs is sponsoring research at three Environmental Hazard Centers; a subset of veterans of the Gulf War are being followed longitudinally for health and psychological symptoms using protocols that address MCS.

- *Develop a case definition for MCS*—The workshops and meetings sponsored by the departments and agencies have all addressed various case definitions. No department or agency is expressly sponsoring an effort to develop a case definition for MCS.

- *Conduct challenge studies*—No agencies of the workgroup are sponsoring or conducting these studies.

IX. Findings and Recommendations

Overview

The public's concern about chemical exposures has historical origins. Many substances that brought great benefits were later found to have long-term risks. Substances such as lead and asbestos were widely used, and their hazards were only slowly identified. The first recognition of concerns usually occurred in highly exposed populations—frequently in occupational settings—among those with readily definable clinical illnesses. For example, the carcinogenic properties of benzene were first identified by the disproportionate occurrence of acute leukemia among persons in certain occupations.

Populations with particular susceptibilities, especially children, have also served to alert public health officials to the dangers of certain chemical exposures. The hazards associated with exposure to leaded paint were first dramatized by clear signs of poisoning in young children who had high levels of exposure because they had eaten paint chips. Now, after decades of use and widespread environmental contamination, the effects of low doses of lead on children are widely recognized. The health of the public as a whole depends on the vigilant monitoring of such emerging diseases and disabilities, regardless of the extent to which medical science is able to explain their origin.

It is appropriate for public health leadership to work to mitigate illness in persons with disorders that are not yet fully explainable. In so doing, it must be recognized that chemical agents found to be noxious by a significant portion of the population may, and often do, present public health hazards that lead to health concerns such as MCS.

Because of the concern for the health and well-being of persons with symptoms of MCS and because MCS presents challenging policy issues, several federal agencies formed a workgroup in 1995 to review the key scientific literature pertinent to MCS, consider the recommendations from various expert panels on MCS, review past federal actions, and develop technical and policy recommendations.

It is currently unknown whether MCS is a distinct disease entity and what role, if any, the biochemical mechanisms of specific chemicals have in the onset of this condition. The workgroup

finds that MCS is currently a symptom-based diagnosis without supportive laboratory tests or agreed-upon clinical manifestations. This dependence on symptom-based diagnosis has resulted in the absence of a uniformly agreed-upon case definition. The workgroup could locate no previously published reports of definite end-organ damage attributable to MCS. However, scientific knowledge changes over time as additional findings are reported; it is therefore important not to lose sight of lessons from the past in which suspected health effects of environmental exposures were verified at a later date through scientific research. A summary of specific findings follows.

Summary Findings

- No single accepted case definition of MCS has been established; proposed definitions all differ in key criteria, and some definitions suggest a broad spectrum of possible symptoms. The validated epidemiologic data required to clarify the natural history, etiology, and diagnosis of MCS are not available.

- Several limitations are found in the design of many published MCS studies. Outcome measures in some studies may be influenced by bias in subject selection, lack of investigator blinding during patient assessment, and inconsistent quality assurance of laboratory determinations. Certain outcome measures (e.g., functional imaging techniques) are investigative research tools and need validation by additional studies.

- The workgroup finds that there are few data on the prevalence of MCS. Only three studies have reported the prevalence of self-reported physician-diagnosed MCS. The prevalence of self-reported physician-diagnosed MCS ranges from published values of 0.2 percent in college students to 4.0 percent in elderly persons and an unpublished value of 6 percent among randomly selected California residents.

- The amount of ongoing MCS-specific research conducted or otherwise supported by the federal government is confined to a limited effort by the National Institutes of Health, National Institute of Environmental Health Sciences (NIEHS). Other than the workgroup on MCS, there appears to be no other federal government group convened expressly to examine MCS as a medical entity of relevance to occupational and environmental health. Although there is ancillary research at NIEHS, the Department of Veterans Affairs (DVA), and the

U.S. Environmental Protection Agency (EPA) concerning the potential relevance of advancing the scientific database on MCS, no federal effort formulates and oversees a collaborative MCS research plan.

- The major recommendations from several expert workshops held since 1990 are still appropriate. These recommendations, if addressed, should advance the public health response to the public's concerns about MCS.

- Information on the fiscal cost of MCS to society is scarce. The fiscal outlay required for or involved in medical diagnosis and treatment of MCS needs additional study.

- Only limited efforts are being made within federal health and environmental agencies to communicate to health-care providers what is known and not known about MCS; these efforts are primarily being made by the Agency for Toxic Substances and Disease Registry (ATSDR). This lack of education for health-care providers is accompanied by increasing public concern about MCS.

- Numerous therapies aimed at treating MCS have been identified in the literature; however, no widely accepted protocols are proven to be effective in addressing MCS symptomatology. Therapeutic interventions that claim to effectively address or minimize these impacts need objective study and validation.

- While study and validation of therapeutic interventions continue, the goal of patient care should be to promote health without causing harm.

MCS as a Public Health Priority

The workgroup was aware of the many demands placed on federal agencies to protect the environment and the public's health. The pressure of constrained budgets and tight personnel ceilings makes it essential that agencies carefully weigh and prioritize research and protective actions directed toward an imposing list of environmental problems.

The workgroup feels compelled, therefore, to comment on MCS in the context of its priority as a

national environmental health problem. Three primary circumstances usually characterize an environmental health issue as being of high priority. First, compelling findings from epidemiologic investigations or surveillance systems can portend consequential health problems in human populations. An example is the identification of the nature and extent of lead toxicity in young children through careful epidemiologic investigations. Second, a priority environmental health problem can be identified through clinical reports verified by the medical community. For example, clinical reports of pesticide poisonings helped shape the understanding that contact with certain pesticides can place pesticide applicators at risk. Third, compelling findings from basic biomedical research may identify mechanisms of action that can translate into human health implications. An example is the basic research on the effects of endocrine disruptors and the implications for human reproductive and developmental health. The workgroup commends these criteria for use in developing a strategic plan for MCS.

The workgroup concludes that the subject of MCS is unlikely to receive extensive research support as a single entity. Personnel and budgetary resources are constrained, and federal agencies are attempting concurrently to evaluate a variety of syndromes that can have disabling symptoms but lack objective clinical or laboratory evidence of disease. Examples include CFS, fibromyalgia, and Persian Gulf War-related illnesses, and diseases diagnosed as chronic subclinical infections.

The workgroup identified the need for an overall strategic plan for these syndromes, including MCS, because of scientific uncertainties and unclear public health relevance that attend each syndrome. The strategic plan should articulate the goals and objectives of the research effort, offer guidance on the priorities and sequence for studies, present the critical elements of study design, and reflect on appropriate resource levels. Those involved in the strategic planning process for research should have a broad range of knowledge and experience and represent a variety of scientific disciplines. Public input should be a vital component of this process.

The workgroup determined that the strategic plan should consider the following recommendations with regard to MCS research:

Research Recommendations for Consideration

- Comprehensive biomedical and clinical research is necessary for a consensus case definition

of MCS that can be used in epidemiologic studies and clinical evaluations. This research needs to include the study of individual MCS patients under controlled conditions. The workgroup encourages a directed effort in this area, recognizing that this issue is a matter of policy as well as an issue of research.

- Data on the prevalence of MCS and disability related to MCS remain a key requisite for a more informed prioritization of MCS-directed resources. The workgroup emphasizes the need for data from representative populations selected by valid epidemiologic methods.

- Data on the role of psychosocial factors in MCS need to be gathered. The tools used to obtain this information should be standardized and validated through the use of reference populations, including those with well-established illnesses (e.g., allergies, asthma, porphyria, and pesticide-related illnesses) known or reported to be associated with susceptibility to chemical exposures. Carefully designed studies should be planned to evaluate both the primary and secondary psychological factors in MCS.

- A targeted effort in basic research is needed to explore pathophysiologic mechanisms that might be associated with MCS. The development and refinement of animal models that could help identify biomarkers of susceptibility in humans is particularly important.

- MCS-related research on biomarkers should be directed as quickly as possible toward validation studies in humans. The populations chosen for such studies should have defined health endpoints, including MCS and other conditions (e.g., asthma and autoimmune disorders) in which chemical exposures are suspected contributors.

- Well-coordinated, multicenter studies are encouraged to detect or exclude the subtle effects that may be associated with low exposures and idiosyncratic reactions. Blinded assessment, testable hypotheses, and objective outcome measures are essential to control for experimenter bias. Federal support for MCS-related clinical research will require stringent quality assurance of all tests under study and ongoing review of results by an independent board, such as those established for therapeutic trials.

- Until a consensus case definition is developed, the case definition of MCS used in research studies should be fully operationalized; that is, it must be described in sufficient detail to be reproducible by other investigators seeking to conform or extend published findings.

- Consideration should be given to conducting a project that collects data on MCS-relevant health costs from sources such as states' workers compensation databases, private insurance records, and federal and state health-care programs.

- A process of obtaining direct public input on the research and policy agenda for MCS and enabling public participation in MCS decision making should be established. The workgroup supports the framework for stakeholder involvement developed by the Presidential/Congressional Commission on Risk Assessment and Risk Management (1997). The framework encourages appropriate and feasible stakeholder involvement during all stages of the risk management process. The framework would equally apply to stakeholder involvement in MCS decision making.

- Because there are no widely accepted protocols that have proven to be effective in treating MCS, the therapeutic interventions claimed to be effective need objective study and validation.

- A cross-agency evaluation of federal granting mechanisms should be conducted to ensure that research review systems are appropriate to support basic and applied research on MCS.

Policy Recommendations for Consideration

The scientific literature is currently inadequate to enable determination of the associations between human exposure(s) to chemicals in the environment and the development or exacerbation of MCS. Targeted research would reduce this uncertainty. Increased scientific knowledge about MCS and the role of environmental chemicals will inevitably be put into the context of benefits and risk.

Virtually all chemicals in use convey both benefits and risks. Every technology, no matter how beneficial, can exert a negative impact on some sector(s) of society. Many chemicals have well-established toxicologic and allergenic properties; undoubtedly, others will be found to have adverse

effects in the future. Public health leaders and other risk managers have an obligation to ensure that the benefits of technologies justify the risks. The public health *vision* is health for the entire population. The *reality* of public health will always involve balancing maximum benefit and minimum harm to the public's health and well-being. Risk managers faced with decisions regarding MCS are offered the following policy recommendations by the workgroup:

- Because of the public health issues and challenges presented by MCS, it is recommended that phased efforts be initiated to conduct the targeted research described in the previous section. A phased approach would make the greatest use of available resources, and at the same time, answer key questions such as prevalence and basic mechanisms of action that would guide follow-up research.

- There is a need to better inform the health-care community about MCS. Health agencies should consider a focused, limited effort in clinician education and awareness.

- Persons should not be offered ineffective, costly, or potentially dangerous treatments. Appropriate care for well-characterized medical and psychological illnesses should not be withheld or delayed. The ramifications of recommending functional changes in workplace or home settings should be considered carefully. Persons identified as having MCS also need education about what is known and not known about MCS.

- There is need for a continuing effort in interagency coordination, whether through the workgroup or a successor group.

- An overall strategic plan for MCS and related syndromes is needed. The strategic plan should articulate the research effort and offer guidance on communication and education of health care providers and persons experiencing symptoms of MCS.

- The Environmental Health Policy Committee of the Department of Health and Human Services appears to be an appropriate body for overseeing the development of an improved science database on MCS and attendant public health responses.

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XI. Abbreviations

AAEM:	American Academy of Environmental Medicine
ADA:	Americans with Disabilities Act
AMA:	American Medical Association
ANS:	autonomic servous system
AOEC:	Association of Occupational and Environmental Clinics
ATSDR:	Agency for Toxic Substances and Disease Registry, DHHS
BEAM:	brain electrical activity mapping
BRFS:	California Behavioral Risk Factor Survey
CDC:	Centers for Disease Control and Prevention, DHHS
CDHS:	California Department of Health Services
CFS:	chronic fatigue syndrome
CLIA:	Clinical Laboratory Improvement Act
CNS:	central nervous system
CS:	chemically sensitive
DHHS:	Department of Health and Human Services
DoD:	Department of Defense
DOE:	Department of Energy
DVA:	Department of Veterans Affairs
DVAMC:	Department of Veterans Affairs Medical Center
ECU:	environmental control unit
EEG:	electroencephalography/electroencephalogram
EI:	environmentally triggered illness
EMG:	electromyography/electromyogram
EPA:	U.S. Environmental Protection Agency
HUD:	Department of Housing and Urban Development
IEIs:	idiopathic environmental intolerances
IPCS:	International Program on Chemical Safety
MCS:	multiple chemical sensitivity

2311	MCHS:	multiple chemical hypersensitivity syndrome
2312	NAS:	National Academy of Sciences
2313	NCEH:	CDC's National Center for Environmental Health
2314	NHEERL:	EPA's National Health and Environmental Effects Research Laboratory
2315	NIEHS:	NIH's National Institute of Environmental Health Sciences
2316	NIH:	National Institutues of Health
2317	NIOSH:	CDC's National Institute for Occupational Safety and Health
2318	NRC:	National Research Council
2319	PET:	positron emission tomography
2320	PNS:	peripheral nervous system
2321	SBS:	sick building syndrome
2322	SPECT:	single photon emission computed tomography
2323	TDS:	time dependent sensitization
2324	TILT:	toxicant induced loss of tolerance
2325	UCSF:	University of California at San Francisco
2326	WHO:	World Health Organization

XII. Annex of Research Suggested by Expert Reviewers

In 1997, the workgroup requested that 12 experts in occupational and/or environmental medicine, toxicology, immunology, psychology, psychiatry, and physiology review its draft report. Some reviewers suggested specific research areas that should be pursued. The workgroup chose to preserve the reviewers' research proposals, but without comment on their merits.

- Investigate patients with common characteristics or exposure histories (e.g., similar precipitating events).

- Conduct double-blind, placebo-controlled exposure challenges in an environmental unit to determine the prevalence of symptomatic response in patients with asthma, MCS, chronic fatigue, depression and other conditions.

- Develop a scientifically based quality of life instrument.

- Continue characterization of human cases in order to understand animal models.

- Conduct multi-center studies to assist in understanding nonsubtle effects that occur with low frequency or that result from uncommon exposures in a single geographic area.

- Research on the prevalence of MCS should be given top priority.

- Psychiatric or psychological evaluations are tools for future research.

- Magnetic resonance spectroscopy and functional imaging methodologies can discern brain chemical abnormalities and may elucidate mechanisms responsible for MCS symptom manifestation.

- Exposure studies should involve more than one experimental session.

- Study the prevalence of chemical intolerance in defined psychiatric diagnostic groups and in temporal lobe epileptics.

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